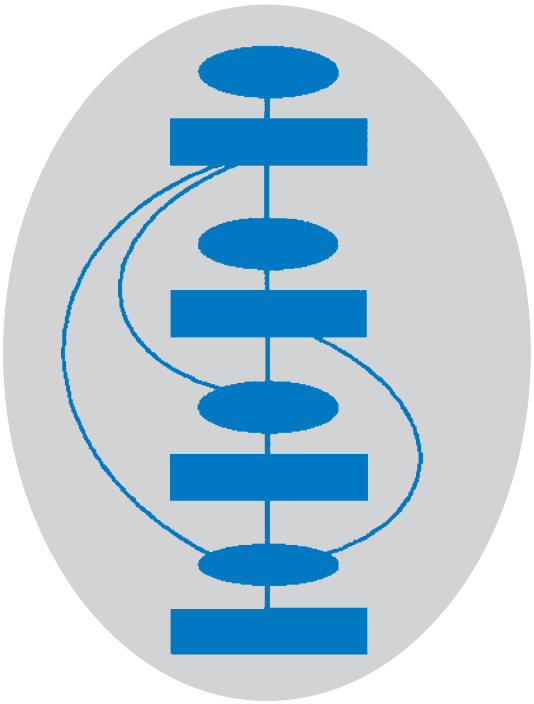
NHS

National Institute for Health and Clinical Excellence

Guidance on Cancer Services

# Improving Outcomes for People with Skin Tumours including Melanoma

## The Evidence Review



Evidence highlighted in grey (pages 120–129 inclusive) has been updated in the full evidence review for: Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal cell carcinomas in the community. NICE guidance on cancer services (2010). Available from www.nice.org.uk/CSGSTIM

February 2006

Developed for NICE by the National Collaborating Centre for Cancer

# Contents

# Chapter 1 - Introduction

This document contains a summary of the evidence reviewed for the production of the recommendations in Guidance for Commissioning Cancer Services – Improving Outcomes for People with Skin Tumours including Melanoma – The Manual. As with previous documents in this series, the topic areas are dealt with in the same order as in the Manual to facilitate cross referencing.

The purpose of the review is to determine the current evidence on interventions and models of care to guide and improve service provision for people with skin cancer.

An assessment of need for cancer services for patients with skin cancer in England and Wales was undertaken as background to this service guidance and is attached as Appendix A.

## Methodology

### Searching for evidence

The stages in the identification and retrieval of evidence are as follows:

#### 1. Clinical question development

The members of the Guidance Development Group (GDG) were asked to consider the issues covered in the project scope and to submit clinical questions covering these issues. A total of 62 questions were submitted to the National Collaborating Centre for Cancer (NCC-C).

#### 2. Literature searching

Systematic search strategies were constructed by the Information Specialist to identify published evidence for the research questions set by the GDG. A

sample search strategy is provided in Appendix C. The search period ended at the end of January 2005.

Unlike clinical guidelines which focus on specific clinical questions, the research questions for this service guidance addressed broad issues of service provision. Consequently there was a wide range of topic areas for consideration. For this reason it was appropriate in some instances to handle several research questions together in a single literature search.

Studies were selected for critical appraisal according to the hierarchy of evidence, (Scottish Intercollegiate Guidelines Network 2002; National Institute for Health and Clinical Excellence 2005) relevance to the research questions and applicability to service provision within the National Health Service (NHS) in England and Wales.

Identified titles and abstracts were initially screened for relevance to the clinical question by the Information Specialist and thereafter by the Researcher. Definite inclusion/exclusion criteria were not employed for articles, because of the nature and variability of the literature on service delivery. Only articles in English were selected for critical appraisal. In some instances help from a member of the GDG was enlisted to verify the relevance of selected articles and as a supplementary check on the completeness of the search. In general no formal contact was made with the authors for each paper identified, but occasionally communication was made for clarification of specific points.

### 3. Critical appraisal

The identified studies were critically appraised and graded for quality using the methodology from the NICE Guideline Development Methods Manual (National Institute for Health and Clinical Excellence 2005) and the information relevant to the question was extracted and entered into the evidence table(s). The evidence grade appended to each study in the evidence table reflects both the study design (e.g. randomised controlled trial (RCT), cross sectional study) and also a judgement of the study methods applied, accepting the study design (i.e. good, fair, poor). In this way the

quality of the evidence to support the recommendations made in the manual is explicit.

Owing to practical limitations the final selection, critical appraisal and data extraction were undertaken by a single Researcher. All tables were circulated to the GDG members for comments. References were also supplied by the GDG members and some stakeholder evidence was used. Both sources were always appraised for quality.

### 4. Synthesising evidence

As a general comment, evidence quality for many of the research questions is poor. There were very few RCTs relevant to the majority of the clinical questions. This is a widely acknowledged problem with health service research and every effort was made to maximise the retrieval of relevant high quality literature. Where available, evidence from good quality systematic reviews was appraised and included in the evidence tables; not all studies in the reviews were individually appraised.

The evidence tables recommended for use in the NICE methodology manual were modified to accept the type of studies identified for service guidance. In addition to the evidence tables a brief evidence summary is provided with each table titled, *Summary of the supporting evidence for the recommendations,* as well as a bullet list of each contributing study. Each evidence table relates to a single search strategy and the relevant research questions are included at the beginning of each section and also at the top of each evidence table. References are included at the end of this document.

## Other sources of evidence

### Expert position papers

The GDG identified areas where there was a requirement for expert input. These areas were addressed by the production of a position paper by a recognised expert. Such experts were identified by contacting the relevant registered stakeholder and asking for a suitable nomination to deal with a

particular topic area. These experts were also a source of advice in identifying relevant studies for appraisal. The position papers were presented at the GDG meetings for discussion. The papers that made a substantial contribution to the evidence are included in Appendices E-J.

Key strategic documents pertinent to skin cancer were also identified as sources of evidence. Relevant national and international guidelines were accepted as sources of evidence and were appraised for quality using the Appraisal of Guidelines Research and Evaluation tool (AGREE).

### GDG member and stakeholder submissions

A small volume of evidence was identified by individual GDG members or by stakeholders during consultation period(s). This evidence, like that from other sources, was critically appraised.

### Health economic evidence

Economic evidence, where it existed, was extracted from the evidence tables and was supplemented with searches performed by the Centre for the Economics of Health, University of Wales, Bangor. This evidence informed the Health Economics Report which accompanies the Manual and this Evidence Review.

### Complementary research

One complementary piece of research was commissioned to elicit the views of patients with skin cancer treated in England and Wales prior to the dissemination of this guidance. A questionnaire survey titled, *The skin cancer patient experience – a report for the NICE skin tumours service guidance* was designed and administered by the GDG and the NCC-C. Data from this study are included in evidence table form in Chapter 2 of this document titled, *Patient centred care* with a full report provided in Appendix B.

## Recommendations

### Drafting recommendations

The GDG members were allocated specific topic areas and asked to review the evidence tables pertaining to the topic and draft recommendations for the service guidance.

### Agreeing recommendations

Once an early draft of the guidance was produced, the GDG members were asked to review the draft document and consider whether:

a) there appeared to be any major gaps in the synthesised evidence.

b) the recommendations were justified from the evidence presented and whether they were sufficiently practical and precise so that health service commissioners and the relevant front line healthcare professionals could implement them.

During the development of this guidance no formal consensus methods were used. Consensus was achieved by informal means during GDG meetings and correspondence outside the meetings.

The absence of high quality evidence for the majority of the clinical questions/topic areas made the grading of the recommendations impractical.

## Writing of the guidance

The first formal draft version of the guidance was coordinated by the Chair and Clinical Lead of the GDG in accordance with the decisions of the GDG. The draft guidance was circulated for consultation according to the formal NICE stakeholder consultation and validation process prior to publication.

# Chapter 2 – Patient Centred Care

## Existing Guidance

The National Institute of Clinical Excellence has issued guidance on *"Improving Supportive and Palliative Care for Adults with Cancer"*. However, patients with skin cancer have specific needs that are not explicitly addressed. Furthermore, the Supportive and Palliative Care guidance applies to *adults* with cancer, whereas the skin cancer guidance is intended for *all* patients with skin cancer including children and adolescents.

The draft NICE Guidelines titled, *Social Value Judgements – Guidelines for the Institute and its Advisory Bodies, Draft for Consultation, April 2005* describe the Institute's approach to incorporating social value judgements into NICE guidance. The guidelines consider moral principles including respect for patient autonomy (including patient choice), and distributive justice. The guidelines also highlight the need for conditions that are associated with social stigma to be given a carefully considered level of priority amongst all healthcare provision.

## Survey of Patients' views

The results of the survey of patients treated for skin cancer undertaken in England and Wales by the Skin Cancer GDG in 2004 are tabulated in Evidence Table 2.9 at the end of this chapter. A full report is included as Appendix B.

## The experiences and needs of patients with skin cancer

### The questions

*What are skin cancer patients' needs?*

*What are the patients' general experiences of being told they have skin cancer?*

**The nature of the evidence**

Twelve studies were identified as follows:

- One systematic review of good quality
- Nine observational studies of fair quality
- One observational study of poor quality
- One expert review of fair quality

Five studies are of UK populations. The remaining studies are from Canada, Australia and the US. Applicability to the UK is therefore limited.

Five studies are of patients with melanoma, three are of patients with cancer, one is of patients with basal cell carcinoma (BCC), two are of patients with skin cancer and the systematic review is of patients in various clinical settings.

**Summary of the supporting evidence for the recommendations**

**There is evidence from observational studies that diagnosis of cancer is a stressful event and that there may be unmet need for support. Observational study evidence suggests that a minority of patients diagnosed with melanoma report moderate to high levels of distress and that this group relies heavily on coping strategies that are of no benefit. Observational study evidence also suggests that higher levels of traumatic stress are experienced by patients with more advanced disease at initial diagnosis and that the experience of skin cancer affects patients' lives in terms of sun awareness. Systematic review evidence suggests that educating patients and clinicians in communication improves patient outcomes.**

- The cross sectional study by Fallowfield et al. (2001) studied doctors' recognition of psychological distress and concluded that much of the probable psychiatric morbidity experienced by patients with cancer goes unrecognised and therefore untreated.

- The longitudinal study by Ford, Lewis and Fallowfield (1995) found that between 26% and 30% of a sample of newly referred patients with cancer scored above the threshold for probable psychiatric disorder on two anxiety scales whereas at 6 months follow-up, levels had fallen to 10% and 21% respectively.

- The controlled, cross sectional study by Holfeld et al. (1990) found that patients with BCC experienced no more psychosocial problems than those seen in members of the general population.

- The cross sectional study by Kelly et al. (1995) found that measures of traumatic stress varied according to disease stage at diagnosis in patients with melanoma.

- The cross sectional study by Trask et al. (2001) found that whilst most patients with melanoma did not report a clinically significant level of distress, 29% reported moderate to high levels of distress. Distressed individuals were found to employ maladaptive coping strategies.

- The cross sectional study by Whelan et al. (1997) found that 33% of patients who had recently been diagnosed with cancer were identified as psychologically distressed.

- The qualitative study by Winterbottom and Harcourt (2004) found that patients with melanoma, BCC and squamous cell carcinoma (SCC) experienced similar levels of anxiety and depression after diagnosis and treatment. Patients with melanoma reflected more on their diagnosis and prognosis and had greater need to adopt coping strategies. The needs for clear information of all patients studied were not always met.

- The systematic review by Stewart (1995) found that communication training of patients and physicians improved patient health outcomes.

- The cross sectional survey by Bonevski et al. (1999) concluded that there is unmet need for information in patients with melanoma and that

younger patients reported greater psychological need than older patients.

- The literature review by Hancock (2003) supported the role of the clinical nurse specialist in meeting the psychosocial support needs of patients with melanoma.

- The observational study by Schofield et al. (2001) found that 47% of patients with melanoma wanted no other person present at the time they were told of their diagnosis, 44% wanted their spouse present and 73% endorsed the option of talking to a counsellor at some time post-diagnosis.

- The multi-centre qualitative survey by the Skin Cancer Guideline Development Group on behalf of NICE (2004) found that whilst a majority of patients with skin cancer reported that they did not have special needs during their treatment, a majority also thought that skin cancer had affected their life, most commonly in terms of sun awareness.

# EVIDENCE TABLE 2.1

## *What are skin cancer patients' needs?*

## *What are the patients' general experiences of being told they have skin cancer?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bonevski *et al.* 1999) | To assess the needs of patients with melanoma including melanoma specific needs. | Cross sectional survey (quantitative). | 179 patients (out of 300 eligible) aged 17 years or older with melanoma diagnosed at least three months before the study: 54% had tumours up to 0.76 mm thick.<br><br>**Australia** | Questionnaire addressed the following items:<br><br>Psychological, health information, physical and daily living, patient and care support, interpersonal communication and 12 additional melanoma-specific items. | 6 of the 10 most common needs rated as moderate to high by patients concerned provision of information (regarding risk of recurrence, further treatment, test results, treatment benefits and side effects). Highly rated service and resource needs concerned car parking, food and drink facilities, library resources on melanoma, monetary allowance for travel, 24 hour telephone support and respite care. Younger patients reported greater psychological need than older patients. Patients who had not visited the clinic for one to two years were 8.8 times more likely to report information needs than patients seen within the previous three months. Patients with recent melanoma diagnosis reported the greatest need for information, care and support and communication. Author concludes that there is unmet need for information in patients with melanoma and states the importance of undertaking assessment of needs specific to cancer type. | 92% of patients reported their tumour removed; hence few were likely to be undergoing medical treatment. | 3 |
| (Fallowfield *et al.* 2001) | To assess the ability of doctors to establish the psychological status of patients during outpatient | Cross sectional comparison of doctors' assessment of | 143 doctors attempted to establish the psychological status | Different tools used to assess psychological status – patients | 36.4% patients had GHQ scores suggestive of psychiatric morbidity. Doctors' sensitivity was 28.87% (SD 25.29), specificity 84.79% (SD 17.44). | Use of VAS for assessing "distress" – were the doctors assessing the same thing as the patients? | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | consultations in cancer centres and hospitals in the UK. | cancer patients' psychological status with patients' self-assessments. | of 2297 patients during consultations in 34 cancer centres and hospitals.<br><br>**UK** | completed the 12 item General Health Questionnaire (GHQ-12); doctors completed a visual analogue pain scale (VAS) designed to capture their perceptions of patients' distress at the end of the interview. | Misclassification rate was 34.7% (SD 13.79).<br>True positive patients had significantly longer consultations than those who were false negatives.<br>Much of the probable psychiatric morbidity experienced by patients with cancer goes unrecognised and therefore untreated. | Doctors blinded to patients' GHQ scores but they were aware the assessment was being made.<br><br>Part of larger study – randomised trial of a communication skills training programme for cancer specialists. Generalisability to other doctors? | |
| (Ford *et al.* 1995) | To investigate the levels of psychological distress in a heterogeneous group of newly referred out-patients with cancer. | Longitudinal cross-sectional observational study. | Heterogeneous group of 117 newly referred outpatients in an oncology department of a London teaching hospital; either newly diagnosed (primary bad news) or else patients with an established diagnosis in whom initial treatment had been unsuccessful (secondary bad news).<br><br>**UK** | Demographic data; Levels of psychological distress using GHQ-30 and Hospital Anxiety and Depression Scale (HADS) measured at baseline, after 1 month and after 6 months.<br>Those with partners completed the Golombok-Rust Inventory of Marital State (GRIMS) at 6 months. | At the first assessment 30% of the sample scored above the threshold for probable psychiatric disorder on the GHQ-30 and 26% on the HADS scale. At 6 months follow-up levels had fallen to 21% for the GHQ-30 and 10% for HADS anxiety. The numbers of probable cases of HADS depression was 7% at the first assessment and 5% at follow-up. Differences in levels of psychological morbidity according to age, sex, partner status and socioeconomic group were demonstrated. | No firm conclusions as to whether differences in levels of psychological morbidity were independent of each other as a controlled multivariate analysis of the data set was not possible. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Hancock D 2003) | To review the literature about psychosocial needs of patients with melanoma and describe how these needs can be supported through the role of the clinical nurse specialist (CNS). | Unsystematic review/ discussion paper. | Patients with melanoma.<br><br>**UK** | • Recommendations based upon literature review. | Review leads to the following recommendations:<br>• The CNS should assess and document the psychosocial support needs of patients with melanoma at time of diagnosis and throughout their cancer journey.<br>• Patient held records should be available to aid the 'two-way' communication process.<br>• Written information should be compiled by a multidisciplinary group and include issues relating to diagnosis, treatment, recurrence, self-examination and sun safe behaviour and a flow chart illustrating the melanoma journey.<br>• Information sheets added to the patient held notes should be according to stage of melanoma and requirement of the individual patient.<br>• A CNS information sheet to include contact details and the support service offered should be available from time of diagnosis<br>• Protocols should be written for the proposed CNS follow-up service for patients with thin melanomas. | Review of 5 pieces of evidence. Some relevant literature (and more up-to-date literature) missed.<br>However: recommendations are by an expert and most do seem to follow from the literature reviewed. | 4 |
| (Holfeld *et al.* 1990) | To investigate the psychosocial problems of patients diagnosed and treated for BCC (BCC) as compared to the general population. | Controlled cross-sectional study. | 39 BCC patients from local register and 39 age, sex, residence-matched controls.<br><br>**Canada** | Questionnaire designed to a) assess problems and concerns that BCC patients could encounter in interpersonal relationships and b) assess the impact of BCC on emotional adjustment. | Chi square analysis revealed no statistically significant difference between the BCC patients and the control group.<br><br>No more psychosocial problems were found in BCC patients than in members of the general population. | Appropriate tools?<br>Big difference in marital status between study group and controls.<br>No info on size of lesions; time since diagnosis, recurrences etc.<br>Effect of tool being administered by interview (by whom?) rather than self-administered? | 3 |
| (Kelly *et al.* 1995) | To investigate posttraumatic stress responses to a diagnosis of melanoma and to | Cross-sectional study. | 95 consecutive patients attending an outpatient melanoma clinic. | Self-report: Impacts of Events Scale (examines common traumatic stress | Significant differences among disease stages detected on measures of traumatic stress response to the diagnosis of melanoma ($p < 0.001$ – | Title suggested that study was conducted AT diagnosis – but time from diagnosis varied significantly between groups. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | validate use of the Impact of Event Scale (IES) as a measure of response to the trauma of life-threatening disease. | | **Australia** | symptoms); HAD (examines affective and cognitive symptoms of depression in a medically ill population); GHQ (somatic symptoms, social dysfunction, anxiety, severe depression). | Stage III>Stage I); measures of anxiety and depression failed to discriminate between stages. | Sampling bias? Excludes non-surviving patients. | |
| (Schofield *et al.* 2001) | To investigate patient preferences for communication practices and to identify any disparities between guidelines, patient preferences and patient recollections of hearing their diagnosis. | Observational study.<br>Self-report questionnaire designed to elicit information about experiences and preferences with communication at the time of diagnosis concerning prognosis and treatment.<br>Compared with published guidelines. | Consecutive sample of 131 newly diagnosed patients with melanoma (diagnosis within 4 months of study).<br><br>**Australia** | Patients' preferences and experiences. | **Support preferences:** 47% wanted no-one else present at time told of diagnosis; 44% wanted spouse present. Only 1 person wanted another doctor present and no-one wanted a nurse or social worker present. 73% endorsed option of talking to a counsellor at some time post-diagnosis.<br><br>Current Australian recommendations on how to communicate a diagnosis of cancer were generally supported by patients' expressed preferences. | Recognises the potential recall bias / sampling bias of subjects 3-4 years post-diagnosis and using the same instrument containing additional items generated from focus groups and a literature review. However, non-validated instrument used to gather data. | 3 |
| (Skin Cancer Guideline Development Group on behalf of NICE 2004) | To measure the experience of patients with skin cancer in the UK. | Multi-centre qualitative survey | 94 patients with skin cancer of different types: melanoma (55), non-melanoma (24), unclassified (11), missing data (4).<br><br>Age range reported categorically – the majority of patients were aged between 30 and 70 years.<br><br>**UK** | Patients reported experience of diagnosis, referral, treatment and follow-up and their reported associated emotions.<br>Patients' reported need for information and support. | **Quantitative results**<br>• 37/91 patients sought advice from a person other than their general practitioner (GP), including their partner, family and friends in the vast majority of cases.<br>• 32/89 patients reported feeling 'worried' when they first thought that something was wrong with their skin.<br>• 53/90 patients were invited to bring a relative to appointments for support.<br>• 66/80 patients did not report special needs during their treatment. Of those who reported needs, needs were met in 12/14 of patients. | Data missing for a proportion of patients for many outcomes, therefore denominators in proportions are based upon patients for whom data are available in each case. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | • 61/75 of patients did not have any difficulty in accessing services for skin cancer.<br>• The most commonly reported professionals that patients wanted to see at appointments were consultants, doctors and nurses.<br>• 63/87 patients thought that skin cancer had affected their life, most commonly in terms of sun awareness. | | |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Stewart 1995) | To ascertain whether the quality of physician-patient communication makes a significant difference to patient health outcomes. | Systematic review of RCTs and analytical (observational) studies.<br>Interventions:<br>In RCTs, interventions to improve communication approaches. These interventions consisted of seminars, training sessions, information packages, taped messages, patient education and different patient information approaches.<br>Analytical (observational) studies involved the observation of communication behaviours without altering them.<br>Communication was classified as relevant either to history-taking or to discussion of the management plan, or 'other' when it did not fit into either of these two categories. | 21 studies were included, of which 11 were RCTs and 10 were analytical (observational) studies. The total number of participants (patients) was 3,753. In addition, a total of at least 312 physicians participated in the review, as specified in 15 studies.<br><br>Results not combined.<br><br>Review undertaken in Canada | Patient health outcomes as measured by physiological status, functional status, symptom resolution, and emotional status. | Studies of history-taking (4 RCTs involving 1,349 patients and 4 analytical studies involving 614 patients): education of both the patient and physician was found to improve patient health outcomes. Of the 8 studies, 7 showed significant positive findings, and 1 (an analytical study) a non-significant result.<br>Studies of the discussion of the management plan (7 RCTs involving 1,251 patients and 8 analytical studies involving 1,025 patients): patient education was found to influence both emotional and physiological status, whilst physician education was found to influence emotional status. All of the RCTs and 6 of the analytical studies found significant correlations between communication interventions or variables and patient health outcomes.<br>Studies of other aspects of communication and patient health outcome (3 RCTs with 600 patients and 1 analytical study with 242 patients) were inconclusive. | Most of the studies demonstrated a correlation between effective physician-patient communication and improved patient health outcomes.<br><br>Although aspects of study quality are mentioned briefly, the studies do not appear to be formally weighted according to their quality. There is little information concerning decisions for selection of studies and data abstraction.<br>Included studies may be of poor quality – little information as to how quality was assessed.<br><br>Only 1 database searched. English language only. Unpublished articles included. | 1+ |
| (Trask *et al.* 2001) | To identify levels of distress present in individuals seeking treatment at a large, multidisciplinary melanoma clinic. To determine the quality of life, level of anxiety, and | Cross-sectional study. | 178 melanoma patients with Stage I-III disease at one centre (aged 22-86). Assessments made at initial consultation. | Brief Symptom Inventory (measure of emotional distress); SF-36 (assesses health functioning – surrogate for quality of life); | Most patients did not report a clinically significant level of distress, 29% reported moderate to high levels of distress. Distressed individuals associated with maladaptive coping strategies e.g. escape-avoidance coping and poorer quality of life. | Authors conclude that although most individuals do not present with significant levels of distress, a significant minority are distressed and rely more heavily on coping strategies that do not benefit them. Such individuals would | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | coping strategies used by individuals with melanoma before treatment. | | **US** | Ways of Coping (assesses individual coping processes); State-Trait Anxiety Inventory (assesses transient or situational and stable or dispositional symptoms of anxiety). | | likely benefit most from psychological intervention. | |
| (Whelan *et al.* 1997) | To examine the physical and emotional health status, self-perceived problems, and needs of newly diagnosed cancer patients to determine and plan supportive care strategies. | Cross-sectional observation study. | 134 newly diagnosed cancer patients attending a regional cancer centre (including 15% non-melanoma patients) interviewed prior to first appointment in clinic.<br><br>**Canada** | Physical health status (Symptom Distress Scale); psychological health status (GHQ); day-to-day functioning (Rapid Disability Scale); social support (modified Sarason's Social Support Scale). Self-report of needs. | 96% reported current symptoms including fatigue (66%), worried outlook (61%), difficulty sleeping (48%) and pain (42%). 33% were identified as psychologically distressed with a GHQ score >6. 85% had information needs, 66% indicated>1 social concern and 41% reported need for assistance with day-to-day living. | No information on e.g. co-morbidity which could impact on self-reported data. How much due to the newly-diagnosed cancer and how much due to other factors? | 3 |
| (Winterbottom & Harcourt 2004) | To explore patients' early experiences of skin cancer, including how they cope with the diagnosis, and to give suggestions for improved care provision. | Qualitative study based on interviews with patients. Questions designed to explore patients' journeys through the process of diagnosis and treatment. Thematic content analysis undertaken. | 8 women and 8 men aged between 24 and 90 years. 7 patients had BCC, 4 had SCC and 5 had melanoma. Participants had relatively non-invasive/lower risk tumours. Time from diagnosis to interview ranged from 3 to 48 months. Participants recruited from a dermatology centre.<br><br>**UK** | Patients' accounts of their experiences of diagnosis and treatment. | **BCC and SCC:** Provision of information important to how the diagnosis affected patients. Patients made causal attributions but were unsure of the underlying cause of disease. Patients expressed satisfaction with the care they had received, which appeared to minimise the impact of the experience.<br><br>**Melanoma:** Similar to BCC and SCC, patients minimised the experience, which was found to have no long lasting effects on their lives. However, these patients used a wider variety of coping strategies, in particular after diagnosis and before and during treatment. Melanoma appeared to have a more profound impact upon their lives.<br><br>Author concludes:<br>• Patients with melanoma, BCC and | The 16 patients interviewed had relatively non-invasive disease: treatment for all but one patient required removal of the lesion alone. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | SCC experience similar levels of anxiety and depression after diagnosis and treatment.<br>• Patients with melanoma reflected more on their diagnosis/prognosis and had greater need to adopt coping strategies.<br>• The needs of all patients studied for clear information were not always met and this has implications for nurses involved in their care. | | |

# The information needs of patients with skin cancer

### The questions

*What are the information needs of patients at diagnosis of skin cancer?*

*How should information be provided to patients with skin cancer?*

### The nature of the evidence

Twenty three studies were identified as follows:

- Four systematic reviews of good quality.
- Three RCTs, one of good quality and two of poor quality.
- One non-randomised intervention study of fair quality.
- Nine observational studies, three of good quality, four of fair quality and two of poor quality.
- Two clinical guidelines of good quality.
- Three expert literature reviews of good quality.
- One expert opinion article.

Seventeen studies originate from the UK, so applicability to the UK is good. Two studies are from Australia, two from Canada, one from the US and one is from Sweden.

Eight studies are of patients with skin cancer, of which six are of patients with melanoma. Eight studies are of patients with cancer. Two studies are of healthcare professionals. One study is of women patients with breast cancer and four studies are of patients in non-cancer specific healthcare settings.

### Summary of the supporting evidence for the recommendations

### The information needs of patients at diagnosis of skin cancer

**Evidence from observational studies and expert review / expert opinion suggests that a high proportion of patients with cancer report needs for information, on diagnosis, prognosis, treatment and likely impact of the disease on work and family life. In patients with melanoma, the need for information is high at the time of diagnosis, although patients can have poor understanding due to emotional state. Evidence suggests that patients with melanoma are concerned about the risk of recurrence. The studies identified, which report on the extent of unmet need for information in patients with cancer, do not reach consensus, although studies report that inadequate information is the commonest cause of patient dissatisfaction and that an important supportive role exists for the clinical nurse specialist.**

- The cross sectional survey by Bonevski et al. (1999) found that the majority of needs reported by patients with melanoma concerned provision of information regarding risk of recurrence, test results and treatment. The greatest need for information and support was in patients with recently diagnosed melanoma.

- The expert review by Coulter (2003) concluded that inadequate provision of information to patients with cancer is the commonest cause of patient dissatisfaction and that both provision of information and the extent to which patients are involved in clinical decision making, should be individualised.

- The small, cross sectional study by Leadbetter (2001) investigated the quality of information given to patients with cancer and found that patients can have poor understanding due to emotional state and recommended that information should be provided at the patient's own pace.

- The cross sectional survey by Luker et al. (1995) found that women patients with breast cancer reported priority needs for information about likelihood of cure, spread of disease and treatment options.

- The cross sectional survey by Meredith et al. (1996) found that patients with cancer wanted to know their diagnosis and most also wanted to know the chance of cure and the side effects of their treatment.

- The questionnaire survey of patients with a recent diagnosis of melanoma by Schofield et al. (2001) found that the majority of patients wanted information about diagnosis, life expectancy, effect of the disease on work and family life and treatment. The majority also wanted supplementary written information, and valued being seen 'face-to-face'.

- The letter of expert opinion by Slowie (1999) reported that patients in primary care commonly thought that doctors did not provide an environment in which they would feel free to ask questions, because doctors' time is limited and practices are busy and crowded.

- The cross-sectional study by Whelan et al. (1997) found that 85% of patients newly diagnosed with cancer reported information needs.

- The qualitative study by Winterbottom and Harcourt (2004) found that there was unmet need for information at the time of diagnosis.

- The multi-centre qualitative survey by the Skin Cancer Guideline Development Group on behalf of NICE (2004) found that the commonest reported needs for information at diagnosis concerned treatment, seriousness of condition, potential for spread, recurrence and risk of mortality. The majority of patients reported that the amount of information provided was 'about right', that they understood what was said, but that there was insufficient time at the consultation.

- The audit undertaken through the use of focus groups of patients with melanoma by Wright et al. (2004) found that many patients reported feelings of shock and blankness when learning of the diagnosis. There was great variation between patients in terms of information requirements whereas most found written information useful. The importance of support by clinical nurse specialists was also affirmed.

**Information provision to patients with skin cancer**

**There is systematic review evidence that provision of information to patients with cancer can improve patient outcomes. The same level of evidence also**

**suggests that the provision to patients with cancer of summaries or recordings of consultations can assist patient understanding, but there is little evidence for improvement in psychological state as a result. Systematic review evidence suggests that provision of communication training for health professionals in cancer care improves their communication skills and studies of such interventions have reported improvements in clinicians' consultation skills. Observational study evidence is supportive of provision of written information to patients with melanoma. Expert review evidence suggests that improved communication in hospitals improves the effectiveness of care. Evidence based guidelines for melanoma patients produced in the UK are supportive of the provision of appropriate information to patients with skin cancer and also of communication skills training for health professionals.**

- The RCT by Brandberg et al. (1994) found that in patients with melanoma, the intervention group randomised to receive a 1.5 hour, nurse led teaching session with provision of an educational brochure, had greater satisfaction with their information, a higher level of knowledge of melanoma and a lower proportion of patients requesting further information, compared to the control group. There were no differences found between groups in psychological and psychosomatic variables.

- The non-randomised intervention study by Fallowfield, Lipkin and Hall (1998) found that communication skills training courses for senior clinicians in cancer medicine resulted in improved clinician confidence in key communication areas, increased awareness of patients' psychological needs and changes in practice, including provision of communication training for junior clinicians.

- The systematic review by Fellowes, Wilkinson and Moore (2003) found that provision of communication skills training for health professionals in cancer care improves their skill in using focussed and open questions, controlling follow-up interviews and using emotional speech.

- The RCT by McHugh et al. (1995) provided cancer patients receiving an initial diagnosis or worsening prognosis with an audio tape of the consultation. Patients with the audio tape rated it positively and were shown to recall more

information about their illness than control patients, but there was no difference in psychological improvement between groups.

- The systematic review by McPherson, Higginson and Hearn (2001) found that all included studies of interventions concerning provision of information to patients with cancer improved at least one patient outcome, where outcomes included affective states, knowledge, understanding and patient satisfaction. Provision of preparatory written information before attending a first consultation was shown to be beneficial.

- The systematic review by Scott et al. (2003) found that the vast majority of patients with cancer found that recordings or summaries of their consultations were valuable. Recordings or summaries were associated with better recall of information and greater patient satisfaction with the information. No studies detected any statistically significant effect on anxiety or depression.

- The systematic review by Stewart (1995) of studies of communication quality and patient outcomes (in general healthcare settings) found significant associations between communication interventions or variables and patient health outcomes. Patient education was found to influence both emotional and physiological status, whilst physician education was found to influence emotional status.

- The expert review (presented as a bulletin for decision makers in health) by the University of York (2000) recommended that the information needs of patients with cancer be met by provision of personalised information with the opportunity for patient involvement in decisions. The bulletin also recommended provision of training in communication for health professionals.

- The qualitative study by Winterbottom and Harcourt (2004) found that provision of information to patients with skin cancer was important to how patients were affected by their diagnoses.

- The cross sectional survey by Meredith et al. (1996) found that patients preferred a diagnosis of cancer to be given by a hospital doctor.

- The RCT by Fleissig, Glasser and Lloyd (1999) found that providing outpatients with a prompt card of questions to ask during their consultation was not found to influence whether patients asked their questions, although many patients found the prompt card helpful. The study concluded that patients also need encouragement from staff to ask questions.

- The audit undertaken through the use of focus groups of patients with melanoma by Wright et al. (2004) confirmed the benefits of written information for patients with melanoma.

- The report by the Audit Commission (1993) highlighted problems with communication between clinicians, managers and departments and also with provision of information to patients in acute carer settings. The report stated that improved communication can improve the effectiveness of care.

- Guidelines produced by the Scottish Intercollegiate Guidelines Network (SIGN, 2003) recommend that patients with melanoma should receive targeted information throughout their journey of care and that healthcare professionals working with cancer patients should receive communication skills training.

- Guidelines produced by Motley et al. (2003) on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons recommend that patients with SCC should be provided with suitable, written information concerning diagnosis, prognosis and follow-up support and local and national support organisations.

# EVIDENCE TABLE 2.2

***What are the information needs of patients at diagnosis of skin cancer?***

***How should information be provided to patients with skin cancer?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Audit Commission 1993) | To review communication with patients, relatives and carers in the acute hospital setting. | Report (based upon 46 references). | Patients in acute hospital settings in the UK.<br><br>**UK** | Commentary and implied recommendations based upon findings. | **Summary points:**<br>• The need for communication has grown as health-care has become more complex, but provision has not kept up with growing need.<br>• Improved communication can improve the effectiveness of care.<br>• Patients have experienced difficulties with the content of information and the manner in which it has been delivered – commonly there is not enough information.<br>• Information is often untimely, hurried, contradictory and cannot always overcome barriers arising from disability or language.<br>• Patients often do not receive satisfactory responses to their complaints and questionnaires used to measure patients' opinions are often badly designed.<br>• Clinicians, mangers and departments often communicate poorly with one another, and skills and resources for effective communication are insufficient.<br>• The role of guidelines in telling patients about stages of care is | Graded as expert review. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | recommended as is good record keeping.<br>• Written information and signposting to services are recommended.<br>• More significant improvements will require substantial investment and support from outside organisations e.g. consumer groups. | | |
| (Bonevski *et al.* 1999) | To assess the needs of patients with melanoma including melanoma specific needs. | Cross sectional survey (quantitative). | 179 patients (out of 300 eligible) aged 17 years or older with melanoma diagnosed at least three months before the study: 54% had tumours up to 0.76 mm thick.<br><br>**Australia** | Questionnaire addressed the following items:<br><br>Psychological, health information, physical and daily living, patient and care support, interpersonal communication and 12 additional melanoma specific items. | 6 of the 10 most common needs rated as moderate to high by patients concerned provision of information (regarding risk of recurrence, further treatment, test results, treatment benefits and side effects). Patients who had not visited the clinic for one to two years were 8.8 times more likely to report information needs than patients seen within the previous three months. Patients with recent melanoma diagnosis reported the greatest need for information, care, support and communication. Authors conclude that there is unmet need for information in patients with melanoma and states the importance of undertaking assessment of needs specific to cancer type. | 92% of patients reported their tumour removed; hence few were likely to be undergoing medical treatment. | 3 |
| (Brandberg *et al.* 1994) | To study the effects of an information programme for melanoma patients. | RCT<br>Intervention:<br>The programme consisted of a group meeting and a brochure. | 231 patients with Stage I melanoma:<br><br>77 in intervention group and 72 in control group.<br>3rd group (n=67) not interested in participating in intervention, but provided same data.<br><br>**Sweden** | Satisfaction with information and requests for further information; knowledge of melanoma; concern for naevi; psychological and psychosomatic variables.<br>Measured at baseline; at 3 months. | The information group was significantly more satisfied with information, had a higher level of knowledge and a lower proportion requested further information compared with the control group. There were no differences found on the psychological and psychosomatic variables. | Poor design - no power calculations.<br>Comparison with NI group not valid as self-selected, not randomised.<br>No description of randomisation methods.<br>No blinding.<br>Insufficient information about participants characteristics to enable judgement to be made about whether intervention and control groups similar at baseline or whether they were treated equally.<br>Validity of outcome tool? | 1- |
| (Coulter 2003) | To report on the information needs of patients with cancer, discussing shared | Expert review (16 references) presented as editorial. | Patients with cancer.<br><br>**Review undertaken in the UK** | | Key points re: information:<br><br>• Failure to provide sufficient information is the most frequent | Expert review | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | decision making and the use of decision aids. | | | | cause of patient dissatisfaction.<br>• Full information should always be offered, although clinicians should be aware that not all patients desire detailed information.<br>• An increasing number of patients wish to play an active role in clinical decision making, whereas desire for participation has been found to vary with age, education, disease severity and culture.<br>• Clinicians should assess to what extent patients wish to be involved in the decision making process, and decision aids can help patients make specific decisions about screening, prevention and treatment.<br>• Clinicians report enhanced quality of consultations and patient satisfaction where decision aids are used.<br>• Patient involvement in the development of patient orientated material increases the likelihood that the information is relevant and useful. | | |
| (Fallowfield *et al.* 1998) | To determine the communication difficulties experienced by clinicians in cancer medicine and to develop, implement, and evaluate communication skills training courses. | Non randomised evaluation of intervention involving delivery of a course which included structured feedback, video review of interviews, interactive group demonstrations and small group discussions led by trained facilitators. | 178 senior clinicians who attended a 1.5 or 3-day course designed to enhance skills development, knowledge acquisition and personal awareness.<br><br>**UK** | Self-rated confidence in key aspects of communication, attitudinal shift towards more patient-centred interviewing, perceived changes in personal practice, initiation of teaching programmes for junior staff. | Less than 35% of participants had received any previous communication training. Time, experience and seniority had not improved skills.<br>Pre-course problems concerned giving complex information, obtaining informed consent, handling ethnic and cultural differences.<br>Confidence ratings for key communication areas post course were significantly improved ($p < 0.01$).<br>3 months post-course, 95% reported significant changes in their practice and 75% had started teaching initiatives in communication for junior clinicians.<br>Clinicians showed positive shifts in attitudes towards patients' psychological needs ($p = 0.0002$), and were more patient-centred ($p = 0.03$).<br>Resources for educational initiatives are | Phase I of a study to develop communication skills training courses. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | needed to help both patients and their physicians. | | |
| (Fellowes *et al.* 2003) | To assess whether communication skills training is effective in changing behaviour of health professionals in cancer care with regard to communication/ interaction with patients. | Systematic review of RCTs or controlled before and after studies of communication skills training in cancer health professionals, measuring changes in behaviour/skills using objective and validated scales. | Of 2824 references, 3 trials involving 347 health professionals were included.<br><br>**Undertaken in UK** | Trial one: Provision of an intensive 3 day course then assessment of oncology doctors interacting with 640 patients.<br><br>Trial two: provided a modular course then assessed role plays with oncology nurses.<br><br>Trial three: modular and assessed outcomes with clinical and simulated interviews and patient questionnaires. | Of 2824 references, 3 trials involving 347 health professionals were included. One provided an intensive 3-day course then assessed oncology doctors interacting with 640 patients; a second provided a modular course then assessed role plays with oncology nurses; the third was modular and assessed outcomes with clinical and simulated interviews and patient questionnaires. In the first trial, course attendees used more focused questions ($p < 0.005$), focused and open questions ($p = 0.005$), expressions of empathy ($p < 0.005$) and appropriate cue responses ($p < 0.05$) at follow-up than non-attendees. No significant differences were found between attendees and non-attendees for leading questions. From baseline to follow-up, attendees had significantly different changes in rates of leading questions ($p < 0.05$), focused questions ($p < 0.005$), open questions ($p < 0.05$) and empathy ($p = 0.005$). The only observed significant difference in the second trial was that trained doctors controlled the follow-up interview more than untrained doctors ($p < 0.05$). Neither study found differences in summarising, interrupting and checking. The third trial found trained nurses used more emotional speech than untrained counterparts, particularly regarding anxiety and distress. Patients interviewed by trained nurses used more emotional terms but no differences emerged in questionnaires. | Training programmes assessed by these trials appear to be effective in improving some areas of cancer care professionals' communication skills. It is unknown whether this training would be effective if taught by others, nor the comparative efficacy of these programmes. | 1++ |
| (Fleissig *et al.* 1999) | To determine whether provision of a prompt card to outpatients increases the likelihood that they prepare, remember and ask questions during their | RCT. Intervention: Patients provided with prompt card and explanatory letter. Control: Nothing. Other groups followed up | 2386 new outpatients (dermatology 55%, orthopaedic 16%, gynaecology 29%) attending a single hospital aged over | Outcome measures (quantitative scores based upon patients' questionnaire answers and also open answers) are | Completed questionnaires were returned by 64% of patients. 85% had questions to ask prior to attending: about their diagnosis (20%), causes (19%) and treatment (19%), but the help card group were no more likely to prepare questions than the control | Patients referred by participating GP practices and 'block randomised'. Analyses also compared with a pre-intervention historical control group. | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | first consultation. | by questionnaire post consultation. | 16.<br><br>**UK** | of patients' information requirements before, during and after their consultation. | group. During the consultation the help card was not found to influence whether patients asked their questions, however 62% of those who discussed their questions rated their visit highly versus 39% who had not ($p < 0.001$). 22% of patients thought of questions after the consultation with no difference detected between groups. Patients who rated the consultation highly were less likely to have questions afterwards (13 vs. 25%, $p < 0.001$). In dermatology the help card group were less likely to want to talk more about their treatment ($p < 0.01$) or what caused their condition ($p < 0.05$). 88% of the help card group rated their overall care highly versus 81% of the control group ($p < 0.01$). Author concludes that many patients found the help card helpful, but patients also need encouragement from staff to ask questions during consultations. | Half the patients who were sent a help card said they got more out of their consultation as a result, yet few statistically significant differences between the help card group and the other patients were found. | |
| (Leadbetter 2001) | To establish the amount of information patients were given at their initial diagnosis of cancer, what information was beneficial and whether there were any factors that affected individual needs. | Cross sectional study using structured interview. | 6 women and 4 men diagnosed with cancer in the previous 6 months (mean age 61.3 years), having completed planned treatment (radiotherapy, chemotherapy).<br><br>**UK** | Patients' subjective responses to questions on how information was provided, what they understood and their reported reactions. | **Key points:**<br>• 9 patients had been told they had cancer and one further patient, that her lump was malignant. All respondents felt that jargon was not used.<br>• Two patients were unable to understand all of the information given, due to their shocked state: it appeared that understanding was affected by emotional state.<br>• Patients who were unprepared for being told that they had cancer appeared to find the diagnosis more upsetting than those who had suspected their diagnosis of cancer beforehand: it appeared that prior preparation lessened the fear and shock of the diagnosis.<br>• All patients felt that they had coped following the diagnosis of cancer.<br>• 7 patients were given written information and 3 had found some when attending for treatment. 9 patients found this information clear | Sample size 10 patients. Patients recruited into research excluded due to likelihood of additional information provision. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | and useful. Patients were not provided with information in a consistent way.<br>• 9 patients stated they would not consider going to a self help group.<br>• 7 patients felt that their relatives had been involved and given information.<br><br>Author concludes:<br>• Healthcare professionals should avoid giving information when the patient cannot understand or deal with it.<br>• Patients should be able to obtain information about their condition at their own pace. Information should be provided in a consistent way.<br>• Information should be easily accessible. | | |
| (Luker *et al.* 1995) | To establish the priority of information needs of a sample of women newly diagnosed with breast cancer. | Cross sectional survey, comparing women with newly diagnosed with breast cancer and women newly diagnosed with benign breast conditions. | 150 women newly diagnosed with breast cancer (mean time since diagnosis 2.5 weeks) and 200 women controls with benign breast disease.<br><br>**UK** | Importance of specific information needs, as ranked by women with malignant and benign breast disease. | Overall, women ranked information about likelihood of cure, spread of disease and treatment options as the priority of information needs. Information about sexual attractiveness was ranked low in the profile. No significant differences were found between groups for ranking the information needs. In the breast cancer group, women of age <40 and 40-60 years rated information on sexual attractiveness higher than those aged >60 ($p = 0.05$) and older women rated social life information higher than did younger women ($p = 0.03$). All women were found to be consistent in their ranking according to Kendall's coefficient of consistency. Author concludes: women are able to identify their own information needs near the time of diagnosis, although these needs may subsequently change over time. | All subjects were aware of their disease status when completing the structured interview / questionnaire. Subjects were asked to rank information needs by importance. | 3 ++ |
| (McHugh *et al.* 1995) | To test the hypothesis that providing cancer patients with audiotapes of their clinical interviews can improve information | RCT<br>Intervention: Provision of audiotape of consultation. | 117 newly referred cancer patients being given “bad news”. Either newly diagnosed (primary | Self-reported attitudes to tape - experimental group only – measured at 6 months (stage 3) | At 6 months follow-up, tape group patients reported positive attitudes to the audiotape and were shown to recall significantly more information about their illness than did controls – however | No power calculations and small numbers once sub-group analysis is used.<br>Lack of blinding – could have affected patient responses | 1+ |

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| | recall and reduce psychological distress. To identify demographic and clinical subgroups of patients who might derive particular benefit from access to audiotape, in terms of improving GHQ scores. | | bad news) or else patients with an established diagnosis in whom initial treatment had been unsuccessful (secondary bad news). 63 in intervention group 54 in control group.<br><br>Inclusion criteria: Age 21-75, able to speak and write in English and without primary or secondary brain disease.<br><br>**UK** | Information recall measured at 6 months (stage 3) Psychological distress - GHQ and HAD measured at baseline (stage1), at 1 month (stage 2) and at 6 months (stage 3). | this was statistically significant only for 5 of the 9 categories of information examined. Overall improvement in psychological distress at 1 and 6 months follow-up, as measured with the 30-item General Health Questionnaire and the Hospital Anxiety and Depression Scale was no different in the two groups. However, a second-order interaction suggested that poor-prognosis patients were disadvantaged specifically by access to the audiotape, with less improvement in psychological distress at 6 months follow-up than non-tape controls. | No control over intervention – e.g. no stipulation over when tape should be played<br>No control over the consultation – what was said, length etc.<br><br>cf Ford 1994.<br>cf Fallowfield 2001. | |
| (McPherson *et al.* 2001) | To systematically review RCTs that have evaluated methods of information-giving to cancer patients and their families. | Systematic review of 10 RCTs (n=1292). | Heterogeneous cancer patients, families and carers. Studies focusing on one type of cancer were excluded (fears about generalisability). Majority of RCTs included newly diagnosed patients.<br><br>**UK** | Directly related to interventions:<br><br>**Objective measures:**<br>• Knowledge acquisition, recall, understanding, use of educational resources;.<br><br>**Subjective measures:**<br>• Preferences for information, attitudes towards intervention, uncertainty and satisfaction.<br>• Indirectly related to intervention:<br>• Affective | All interventions improved at least one of the outcomes evaluated. Preparatory written information before attending a first clinic appointment shown to be beneficial. Only 2 interventions appeared to improve measures of psychological state. Comparison of different types of computer information showed that access to general cancer information was a significant predictor of patients' levels of anxiety at follow-up. No differences found for mood, pain, satisfaction or health service utilisation. | Some processes of review not reported clearly. Review limited by scarcity of papers meeting RCT inclusion criteria. | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | states, symptom management, expectations, health service utilisation, coping. | | | |
| (Meredith *et al.* 1996) | To assess the needs of patients with cancer for information about their condition. | Cross sectional survey of patients' views by means of semi structured interview with questionnaire, undertaken at a regional cancer centre and two university hospitals in west Scotland. | 250 (93%) of 269 cancer patients aged under 75 years who had been diagnosed with cancer in the last 9 weeks, selected by age, sex, socioeconomic status, and tumour site to be representative of cancer patients in west Scotland.<br><br>**UK** | Questions address preference for information in general and information about particular aspects of their illness and treatment: the specific medical name of their illness, whether it was a cancer, their progress through treatment, their chance of cure, details of all possible treatments, details of all possible side effects, and how the treatment works and also which health professional they would prefer to tell them about their illness. | 196 of the patients (79% (95% CI 73% to 84%)) wanted as much information as possible, 37 (15%) did not want any, and 15 (6%) wanted only good news. Of the 35 affluent patients, 33 (94%) wanted as much information as possible, compared with 113/146 (78%) of patients with average income and 50/69 (72%) of deprived patients (p = 0.014). The patients' responses were not influenced by age, sex, or type of treatment. Only 11 patients (4%) did not want to know if their illness was cancer, and 238 (95%) patients (95% CI 93% to 98%) expressed a need or an absolute need to know. In contrast, 62 (25%) did not want to know the specific name of the illness, and only 74 (30%) indicated an absolute need for this information. The patients also had a strong desire to know the chance of cure and the side effects of treatments, with 226 (90% (95% CI 87% to 94%)) and 235 (94% (95% CI 90% to 97%)) respectively expressing a need or absolute need to know. The patients who were treated radically were more likely to want to know the chance of cure compared with those treated palliatively (p = 0.002). There was a significant linear trend with more affluent patients seeming to want more information (p = 0.034). The patients receiving radical treatment had a greater need for information about side effects than did those being treated palliatively (p = 0.024). There was a strong preference for diagnosis of cancer to be given by a hospital doctor (60% (95% CI 53% to 66%). Author concludes: almost all patients wanted to know their diagnosis, and most wanted | **Key messages:**<br>• We interviewed 250 patients with cancer to find out what information they wanted.<br>• Almost all the patients wanted to know their diagnosis, and most also wanted to know the chance of cure and the side effects of their treatment.<br>• Younger patients, women, and those receiving radical treatment in particular wanted to know more about treatment options.<br>• The overwhelming preference was for the diagnosis of cancer to be given by a hospital doctor.<br><br>The patients were selected by quota sampling to ensure, as far as possible, that they were a representative sample of cancer patients in the whole of west Scotland. The mean time between the diagnosis and interview was 33 days (SD 15). | 3 + |

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| | | | | | to know about prognosis, treatment options, and side effects. | | |
| (Motley *et al.* 2003) | To provide evidence based guidelines on the treatment of patients with SCC on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons. | Clinical guidelines. | Patients with SCC.<br><br>**UK** | Recommendations for clinical practice. | Patients should be provided with suitable written information concerning diagnosis, prognosis and follow-up support, local and national support organisations and, where appropriate, access to a multi-professional palliative care team. | 82 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Recommendations for practice. | Patients should receive targeted information throughout their journey of care.<br><br>Healthcare professionals working with cancer patients should receive communication skills training.<br><br>Health service patient support groups should be structured and facilitated by trained professionals and should incorporate health education.<br><br>Information on all patient support groups should be made easily available to patients.<br><br>Guidelines provide example information sheets. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |
| (Schofield *et al.* 2001) | To investigate patient preferences for communication practices and to identify any disparities between guidelines, patient preferences and patient recollections of hearing their diagnosis. | Observational study.<br><br>Self-report questionnaire designed to elicit information about experiences and preferences with communication at the time of diagnosis, concerning prognosis and treatment. Compared with published | Consecutive sample of 131 newly diagnosed melanoma patients (diagnosis within 4 months of study).<br><br>**Australia** | Patients' preferences and experiences. | **Information about diagnosis**: 69% wanted "everything", 26% wanted a "moderate" amount of information. **Information about life expectancy**: was wanted by 61%; **effect on work and family life** was wanted by 62%. **Information about treatment:** 81% wanted "everything", 16% wanted a "moderate" amount. 63% wanted this information at time of diagnosis, 16% wanted a delay and 22% responded "both times". **Supplementary information about diagnosis:** 63% wanted written information; 23% information on audiotape. 75% wanted a "FAQ" sheet and 13% would have liked an audiotape of the consultation. | Recognises the potential recall bias/sampling bias of subjects 3-4 years post-diagnosis and using an instrument containing additional items generated from focus groups and a literature review. However, non-validated instrument used to gather data. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | guidelines. | | | **Support preferences:** 47% wanted no-one else present at time told of diagnosis; 44% wanted spouse present. Only 1 person wanted another doctor present and no-one wanted a nurse or social worker present. 73% endorsed option of talking to a counsellor at some time post-diagnosis.<br>**Communication strategies**: 62% rated "being told face-to-face" as most important and 65% rated doctor giving extra taped information as least important.<br><br>Current Australian recommendations on how to communicate a diagnosis of cancer were generally supported by patients' expressed preferences. | | |
| (Scott *et al.* 2003) | To examine the effects of providing recordings or summaries of their consultations to people with cancer and their families. | Systematic review of randomised and non-RCTs that evaluate the effects of providing recordings (e.g. audiotapes) or summaries (e.g. letter with reminders of key points) of consultations to people with cancer or their families. | Twelve studies satisfied the selection criteria, but did not all study similar outcomes.<br><br>**Review undertaken in the US** | Information recall/ understanding.<br>Experience of healthcare.<br>Health and well-being. | In 7 studies, between 83% and 96% of participants found recordings or summaries of their consultations valuable. Five out of nine studies reported better recall of information for those receiving recordings or summaries. Four out of seven studies found that participants provided with a recording or summary were more satisfied with the information received. No studies (out of seven) found any statistically significant effect on anxiety or depression. One study evaluated the effects on quality of life, but found no main effects. | The provision of recordings or summaries of key consultations may benefit most adults with cancer. Although more research is needed to improve our understanding of these interventions, most patients find them very useful. Practitioners should consider offering people tape recordings or written summaries of their consultations. Possible Hawthorne effect ion both doctors' and patients' behaviour – positive impact on content of consultations as knew about recording.<br><br>Studies are small and heterogeneous. | 1+ |
| (Skin Cancer Guideline Development Group on behalf of NICE 2004) | To measure the experience of patients with skin cancer in the UK. | Multi-centre, qualitative survey. | 94 patients with skin cancer of different types: melanoma (55), non-melanoma (24), unclassified (11), missing data | Patients reported experience of diagnosis, referral, treatment and follow-up and their reported associated | **Quantitative results**<br>• 30/58 patients reported a delay in being told the diagnosis of skin cancer.<br>• The commonest reported needs for information at diagnosis | Data missing for a proportion of patients for many outcomes, therefore denominators in proportions are based upon patients for whom data are available in | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | (4).<br><br>Age range reported categorically – the majority of patients were aged between 30 and 70 years.<br><br>**UK** | emotions.<br>Patients' reported need for information and support. | concerned treatment, seriousness of condition, potential for spread, recurrence and risk of mortality.<br>• 66/94 patients reported that there was 'not enough time' with health professionals.<br>• 78/91 patients thought that the amount of information provided on their diagnosis was 'about right'.<br>• 68/78 of patients understood everything about their diagnosis.<br>• 49/80 patients were given written information at diagnosis.<br>• 53/90 patients were invited to bring a relative to appointments for support.<br>• The most commonly reported professionals that patients wanted to see at appointments were consultants, doctors and nurses.<br>• 79/90 patients thought that health professionals respected what patients had to say. | each case. | |
| (Slowie 1999) | Letter expressing expert opinion. | Letter | Primary care patients.<br><br>**UK** | Reports on author's experience. | Patients commonly thought that doctors did not provide an environment in which they would feel free to ask questions, because they could tell that the doctor's time was obviously limited: the clinic was crowded, the doctor did not look them in the eye, or the doctor interrupted frequently when they were trying to speak. Patients also said that if they were confident that they could ask questions or seek clarification they would do so. Their suggestions for improvement included posters for waiting rooms that explicitly gave patients permission to ask questions, and checklists of credit card size that they could refer to during consultations as prompts. | Journal correspondence, with response from Fleissig (above). | 4 - |
| (Stewart 1995) | To ascertain whether the quality of physician-patient communication makes a significant difference to patient | Systematic review of RCTs and analytical (observational) studies. | Twenty-one studies were included, of which 11 were RCTs and 10 were analytical | Patient health outcomes as measured by physiological status, functional | Studies of history-taking (4 RCTs involving 1,349 patients and 4 analytical studies involving 614 patients): education of both the patient and physician was found to improve patient | Most of the studies demonstrated a correlation between effective physician-patient communication and improved patient health | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | health outcomes. | Interventions:<br>In RCTs, interventions to improve communication approaches. These interventions consisted of seminars, training sessions, information packages, taped messages, patient education and different patient information approaches.<br>Analytical (observational) studies involved the observation of communication behaviours without altering them. Communication was classified as relevant either to history-taking or to discussion of the management plan, or 'other' when it did not fit into either of these two categories. | (observational) studies. The total number of participants (patients) was 3,753. In addition, a total of at least 312 physicians participated in the review, as specified in 15 studies.<br><br>Results not combined.<br><br>**Review undertaken in Canada** | status, symptom resolution, and emotional status. | health outcomes. Of the 8 studies, 7 showed significant positive findings, and 1 (an analytical study) a non significant result.<br>Studies of the discussion of the management plan (7 RCTs involving 1,251 patients and 8 analytical studies involving 1,025 patients): patient education was found to influence both emotional and physiological status, whilst physician education was found to influence emotional status. All of the RCTs and 6 of the analytical studies found significant correlations between communication interventions or variables and patient health outcomes. Studies of other aspects of communication and patient health outcome (3 RCTs with 600 patients and 1 analytical study with 242 patients) were inconclusive. | outcomes.<br><br>Although aspects of study quality are mentioned briefly, the studies do not appear to be formally weighted according to their quality. There is little information concerning decisions for selection of studies and data abstraction.<br>Included studies may be of poor quality – little information as to how quality was assessed.<br><br>Only 1 database searched. English language only. Unpublished articles included. | |
| (University of York 2000) | To review evidence on provision of information to patients with cancer and shared decision making in cancer care, and also to make recommendations. | Expert review, presented as a bulletin for decision makers in health service. | Patients with cancer.<br><br>**UK** | Large volume of evidence identified, some of which is of high quality. Primary studies assessed for individual outcomes for communicating with patients, informing patients and involving patients in decision making. | Authors recommend:<br>• Patients' information needs must be addressed in order to meet NHS policy goals and individual differences should be taken into account.<br>• Training in communication should be provided for health professionals and evaluated by professional skills and patient outcomes.<br>• Personalised or tailored | Very concise expert review, backed by a large volume of evidence, including RCTs and systematic reviews. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | information is an option where appropriate.<br>• People with cancer should be given the opportunity for involvement in decisions about their treatment and care and decision aids could be considered.<br>• Resources should be made available for programmes for shared decision making. | | |
| (Whelan *et al.* 1997) | To examine the physical and emotional health status, self-perceived problems, and needs of newly diagnosed cancer patients to determine and plan supportive care strategies. | Cross-sectional observation study. | 134 newly diagnosed cancer patients attending a regional cancer centre (including 15% non-melanoma patients) interviewed prior to first appointment in clinic.<br><br>**Canada** | Physical health status (Symptom Distress Scale); psychological health status (GHQ); day-to-day functioning (Rapid Disability Scale); social support (modified Sarason's Social Support Scale). Self-report of needs | 85% of patients reported information needs. | No information on e.g. co-morbidity which could impact on self-reported data. How much due to the newly-diagnosed cancer and how much due to other factors? | 3 |
| (Winterbottom & Harcourt 2004) | To explore patients' early experiences of skin cancer, including how they cope with the diagnosis, and to give suggestions for improved care provision. | Qualitative study based on interviews with patients. Questions designed to explore patients' journeys through the process of diagnosis and treatment. Thematic content analysis undertaken. | 8 women and 8 men aged between 24 and 90 years. 7 patients had BCC, 4 had SCC and 5 had melanoma. Participants had relatively non-invasive/lower risk tumours. Time from diagnosis to interview ranged from 3 to 48 months. Participants recruited from a dermatology centre.<br><br>**UK** | Patients' accounts of their experiences of diagnosis and treatment. | Provision of information was important to how patients were affected by their diagnoses.<br><br>Author concludes:<br>• Patients with melanoma, BCC and SCC experience similar levels of anxiety and depression after diagnosis and treatment.<br>• Patients with melanoma reflected more on their diagnosis/prognosis and had greater need to adopt coping strategies.<br>• The needs of all patients studied for clear information were not always met and this has implications for nurses involved in their care. | The 16 patients interviewed had relatively non invasive disease: Treatment for all but one patient required removal of the lesion alone. | 3 |
| (Wright *et al.* 2004) | To use focus groups to ascertain what information patients with melanoma would like.<br><br>To use the results to | Audit undertaken by focus groups at three locations. | 6-10 patients who had had melanoma per focus group.<br><br>**UK** | Themes identified from focus groups based upon patients' experiences and information needs. | Themes identified included shock and blankness when learning of the diagnosis, with inability to absorb subsequent information. There were variations between patients in their information requirements, from those | Interviews audiotape and transcribed for thematic analysis.<br><br>All groups facilitated by the same researcher. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | adapt information provided to patients in the South West of England. | | | | who wanted as much as possible from the start, to those who just wanted the bare minimum. Most saw written information, which could be taken home and assimilated, or shared with family, as useful. Preparation for side effects of surgery, such as pain and visual aspects, was also felt to be important, as were 'preventative' and after care aspects. The valuable role played by nurse specialists in providing information and support was identified by a number of participants. Authors conclude that the focus groups confirmed the benefits of written information for patients with melanoma and identified themes which it should address. The benefits and importance of support by clinical nurse specialists were also affirmed. | | |

# Patients with disfigurement following treatment for skin cancer

### The question

*What are the needs of patients with disfigurement as a result of treatment for skin cancer?*

### The nature of the evidence

Nine studies were identified as follows:

- One RCT of poor quality.
- One non-randomised intervention study of poor quality.
- Four observational studies, one of good quality, two of fair quality and one of poor quality.
- One service guideline of good quality.
- Two expert review studies of fair quality.

Five studies originate from the UK, including the service guideline and four studies originate from the US. Applicability to the UK is reasonable.

Three studies are of patients with melanoma. One study is of patients with skin cancer, including melanoma. One study is of patients with non melanoma skin cancer (NMSC). Two studies are of patients undergoing surgery for dermatological conditions. One study is of people with facial disfigurement and the remaining study is of nurses who work in specialist head and neck/burns units.

### Summary of the supporting evidence for the recommendations

**There is evidence to suggest that a negative cosmetic impact arises where patients are insufficiently prepared prior to surgery, but there is little evidence to support the use of photographs to achieve thorough preparedness. Evidence is suggestive of a need for thorough patient preparation from the**

**outset and also for teamwork between disciplines. Observational study evidence suggests that the majority of patients who undergo minor surgery for dermatological conditions do not report adverse cosmetic impact, but also that for those who do suffer an adverse cosmetic impact, few are offered help with concealing scars. Evidence from a non-randomised intervention study suggests that nurses are insufficiently prepared to assist patients with disfigurement in social rehabilitation but that training by lay organisations that are closely in touch with patients can improve these skills. The same level of evidence suggests that interventions for people with facial disfigurement are effective in reducing anxiety and improving confidence in social situations.**

**Evidence from a UK service guideline on plastic surgery supports a patient focussed approach to uniform, ratified, high quality healthcare, also recommending that carers receive support.**

- Service Guidelines produced by the British Association of Plastic Surgeons and NHS Modernisation Agency (2005) are supportive of a patient focussed, rather than specialty focussed model of care, recommending that patients be partners in their own management and also that carers receive support.

- Cassileth et al. (1983) found that factors related to negative cosmetic impact were severity of scar and extent to which patients were unprepared for the actual size of their scars.

- The RCT by Cassileth et al. (1984) strengthened the above finding and further found that the use of photographs as a means to prepare patients for cosmetic impact of surgery did not increase the accuracy of patients' expectations of their postoperative appearance. The photographs were also found to have no effect on levels of preoperative or postoperative distress.

- The survey and non-randomised intervention study by Clarke and Cooper (2001) found that nurses working in specialist units were less prepared to assist in social rehabilitation for patients with disfigurement than physical rehabilitation. Self perceived social rehabilitation skills improved significantly following a training programme.

- Eshima et al. (1996) reports that for the majority of patients with melanoma, surgical treatment with primary closure or skin grafting is the optimal mode of treatment. The more complex plastic surgery techniques are particularly useful for reconstruction of the head and neck region and for extensive surgical defects.

- Kearney et al. (2001) found that the majority patients who underwent minor surgery for dermatological conditions (70%) reported their scar as either invisible or better than expected. 9% rated their scar to be worse than expected. Dissatisfaction was associated significantly and independently with excision from back, younger age and benign histology.

- Lemon et al. (1997) highlight the importance of talking to patients prior to surgery for skin cancer where the use of facial prosthetics is anticipated, in order to thoroughly prepare them for the experience. The importance of a collaborative approach between different professionals is also stressed.

- The survey and non-randomised intervention study by Robinson, Rumsey and Partridge (1996) found that a social interaction skills workshop for people with disfigurement was associated with reduced scores on scales of anxiety and social avoidance at both six weeks and six months follow-up.

- The multi-centre qualitative survey by the Skin Cancer Guideline Development Group on behalf of NICE (2004) found that 44/56 patients were not offered make-up to conceal scars after treatment, whereas 15/44 patients would have liked this.

# EVIDENCE TABLE 2.3

## *What are the needs of patients with disfigurement as a result of treatment for skin cancer?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (British Association of Plastic Surgeons & NHS Modernisation Agency 2005) | To provide guidance for patient-centred models of care in the overlap areas between Plastic, Reconstructive and Aesthetic Surgery and Dermatology. | Service guideline. | Patients with skin conditions for whom Plastic Surgeons have an input to care.<br><br>**UK** | Recommendations for practice. | *Action on Plastic Surgery* programme is supportive of a patient, rather than specialty, focused model of care.<br><br>In the area of plastic, reconstructive and aesthetic surgery and dermatology the public should:<br>• Be educated in the prevention and awareness of early indicators of skin cancer - e.g. "SUNSMART Campaign".<br>• Be supported to undertake self-examination and mole monitoring at regular intervals.<br>• Become responsible partners in their own management.<br>• Be entitled to nationally uniform, ratified, high quality health-care.<br><br>Guidance recommends that patients should be:<br>• Entitled to expect that their carers will also receive support.<br>• Entitled to appropriately set and managed expectations. | Part of a larger strategy for the planning and delivery of patient-centred Plastic Surgery services within the NHS, titled, *Action On Plastic Surgery (AOPS) Programme.*<br><br>AOPS started in 2002 and has put in place 19 AOPS Pilot Site Projects in England and Wales, 18 funded by the Department of Health (England) and one funded by the Welsh Assembly.<br><br>Associated work has been undertaken in Scotland. | 4 ++ |
| (Cassileth *et al.* 1983) | To investigate the | Cross-sectional | 176 patients with | Opinions of the size | Two factors were significantly related to | Authors suggest that primary | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | relationship between primary versus grafted closure for melanoma and the cosmetic impact on the patient of the resulting scar. | observational study. Purpose-designed self-report questionnaire. | melanoma (Stage 1 n=158; Stage II n=16; Stage III n=2).<br><br>**US** | and cosmetic implications of their excisions. | negative cosmetic impact: severity of scar indentation (but not scar length) and extent to which patients were unprepared for the actual size of their scars. Patients whose scars were deeply indented as well as those whose scars were larger than anticipated displayed greatest distress about their appearance.<br>Cosmetic impact was greater for women than for men. | closures, rather than closures requiring skin grafts, have important psychological benefits for patients and that physicians can assist postoperative adjustment by giving patients accurate information about the expected appearance of their scars. | |
| (Cassileth *et al.* 1984). | To test the hypothesis that preoperative preparation of patients for the eventual appearance of their scars would diminish postoperative distress. | RCT<br><br>Intervention:<br>I = 50 were shown 3-6 overview photographs of scars similar in location, size and appearance to that anticipated for them.<br>C = 49 did not see any photographs.<br><br>Outcomes measured at baseline and follow-up at 6 months after surgery. | A total of 99 adult patients scheduled for resection of stage I melanoma attending a pigmented skin lesion clinic.<br><br>I = median age 44 years; 42% M; 76% primary surgical closure,; 24% skin graft.<br>C = median age 47 years; 51% M; 80% primary surgical closure, 20% skin graft.<br><br>**US** | Preoperative and post-operative expectations of the size and cosmetic implications of their excisions. | Patients were least distressed postoperatively when their scars were not larger than anticipated. However, photographs failed to achieve the expected benefit of increasing the accuracy of patients' expectations of their postoperative appearance. Photographs had no effect on levels of preoperative or postoperative distress. | • Improper randomisation alternate consecutive assignment.<br>• No evidence of any blinding.<br>• No power calculations – lack of effect could be due to sample size.<br>• No tests to ensure comparability of 2 groups at baseline.<br>• Insufficient information to assess whether 2 groups treated in same way apart from intervention.<br>• No information about drop-outs Adequacy of follow-up? Scar may alter beyond 6 months. | 1- |
| (Clarke & Cooper 2001) | To investigate the training needs of specialist nurses working with patients who have disfiguring conditions. To measure the effect of an educational intervention for nurses. | Study 1: Cross sectional questionnaire survey.<br><br>Study 2: Before and after intervention study. Intervention = training in psychosocial issues arising from disfigurement, | Specialist nurses working in head and neck surgical units and burns units.<br><br>**UK** | Nurses' perceived skill at social and physical rehabilitation at baseline, and also following a training intervention. | Study 1: For head and neck nurses the mean score for rehabilitation classed as 'social' items were significantly lower than the mean score on 'physical' rehabilitation items ($p < 0.001$). For burns nurses the mean score on social rehabilitation items was significantly lower than the mean score on physical rehabilitation items.<br><br>Study 2: All scores for social items showed a significant improvement except for eating out, which approached | Study 1: 83 questionnaires were returned in total, from burns and head and neck units. Some questionnaires discarded due to suspect response bias (i.e. same boxes ticked throughout).<br><br>Study 2: 10 head and neck nurses randomly selected. 8 nurses attended for the intervention. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | provided by *Changing Faces.* | | | significance. For physical items improvement was seen only in food preparation and advice about resuming housework. Qualitative responses from the nurses valued the intervention. Author concludes: nurses find themselves insufficiently prepared at baseline to provide social rehabilitation for patients with disfigurement, and that perceived skill increases following an intervention developed by a lay led organisation. | Head and neck nurse subjects already known to researchers though database. | |
| (Eshima 1996) | To review the role of plastic surgery in the treatment of melanoma. | Expert review. | Patients with melanoma.<br><br>**US** | | Author states that for the majority of patients with melanoma today, surgical extirpation with primary closure or skin grafting is the optimal mode of treatment. The more complex plastic surgery techniques are particularly useful for reconstruction of the head and neck region and for the extensive surgical defects that require more than the conventional methods of reconstruction. | | 4 |
| (Kearney *et al.* 2001) | To evaluate patients' own assessment of the cosmetic outcome of minor dermatological surgery procedures. | Cross sectional survey. | 207 excisions in 193 patients at a district general hospital (including 40% malignant histology).<br><br>**UK** | Patient satisfaction with scar appearance. | 79% response rate. 70% reported scar to be either invisible or better than expected. 9% rated it to be worse than expected. Dissatisfaction was associated significantly and independently with excision from back, younger age and benign histology. | | 3 |
| (Lemon *et al.* 1997) | To discuss aspects of planning for use of prosthetics for the nose, ear and eye following ablative surgery for non melanoma skin cancer (NMSC). | Expert review. | **US** | | Aside discussion on technical aspects of procedures the authors note:<br>• The initial priority is complete surgical control of the tumour.<br>• The patient should be counselled at the start of definitive treatment to discuss the need for a prosthesis and how it will affect their life in order to promote clear understanding of the outcome.<br>• Teamwork between disciplines is necessary at every stage of the process of surgery and creation of the prosthesis. | | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| (Skin Cancer Guideline Development Group on behalf of NICE 2004) | To measure the experience of patients with skin cancer in the UK. | Multi-centre, qualitative survey. | 94 patients with skin cancer of different types: melanoma (55), non-melanoma (24), unclassified (11), missing data (4).<br><br>Age range reported categorically – the majority of patients were aged between 30 and 70 years.<br><br>**UK** | Patients reported experience of diagnosis, referral, treatment and follow-up and their reported associated emotions.<br>Patients' reported need for information and support. | **Quantitative results**<br>• The commonest treatments received were surgery, excision and chemotherapy / radiotherapy.<br>• 44/56 patients were not offered make-up to conceal scars after treatment, whereas 15/44 patients would have liked this. | Data missing for a proportion of patients for many outcomes, therefore denominators in proportions are based upon patients for whom data are available in each case. | 3 - |
| (Robinson *et al.* 1996) | To investigate the effect of a social interaction skills workshop on the psychological well being of people with facial disfigurement. | Questionnaire survey: 'before and after' intervention. Intervention was a social interaction skills workshop. | 64 people with disfigurement: 23 males and 41 females. All but two participants had facial disfigurement.<br><br>**UK** | Quantitative scores for Hospital Anxiety and Depression Scale (HAD), Social Avoidance and Distress Scale (SAD) and qualitative responses to open ended questionnaire before, at 6 weeks and at 6 months post intervention. Analysis was by Tukey Honestly Significant Difference Test (HSD). | The high levels of anxiety evident prior to the workshop fell significantly 6 weeks post-workshop (HSD = 1.297, $p < 0..01$) and remained significantly lower at 6 month follow-up (HSD = 1.563, $p < 0..01$). Similarly, SAD scores fell significantly at 6 weeks (HSD = 1.89, $p < 0.05$) and again at 6 month follow-up (HSD = 2.26, $p < 0..01$). 6 weeks post-workshop, participants reported feeling more confident in the company of strangers (HSD = -1.266, $p < 0..01$) and about meeting new people (HSD = -1.159, $p < 0..01$). This increase in confidence was maintained at 6 months (HSD = -1.068 and -1.042 respectively, $p < 0..01$ for both). 61% of those who experienced problems before the workshop reported a positive change in these situations. Authors conclude that there is a continuing need to address the psychosocial issues around facial disfigurement. | 47 participants were self referrals and 17 were clinical referrals. 42 non respondents were found to not differ significantly for known psychological and demographic variables. | 3 + |

# Psychological interventions in the care of patients with skin cancer

### The questions

*Does involvement of a psychologist improve patient experience of skin cancer?*

*Does involvement of a psychiatrist improve patient experience of skin cancer?*

### The nature of the evidence

Twelve studies were identified as follows:

- Three systematic reviews or meta-analyses of good quality
- Four systematic reviews or meta-analyses of poor quality
- Four RCTs of poor quality
- One observational study of fair quality.

One systematic review and one meta-analysis were undertaken in the UK but no primary studies identified in this review originate from the UK. The majority of studies (seven) were undertaken in the US and one study each was undertaken in Australia, Austria and Denmark. Applicability to the UK is therefore limited.

The majority of studies (eight) are of patients with cancer. Three RCTs are of patients with melanoma and the observational study is of patients with skin cancer.

### Summary of the supporting evidence for the recommendations

**The majority of studies identified report benefits for patients with cancer, arising from psychological, educational and supportive interventions, with a high proportion of systematic reviews or meta-analyses. Few studies reviewed were inconclusive. The types of intervention studied include psychosocial, educational and supportive interventions. Many studies report improved outcomes for affective symptoms and/or physical symptoms. Other benefits include improved coping and better acquisition of information. RCT evidence is**

**suggestive of improved survival in patients with melanoma through a psychiatric intervention which included health education. One meta-analysis and one qualitative study concluded that disease-specific psychological interventions should be provided for patients with melanoma.**

- The systematic review by Barsevick et al. (2002) found that psycho-educational interventions reduce depressive symptoms in patients with cancer and concluded that behaviour therapy or counselling, either alone or in combination with cancer education, is beneficial.

- The systematic review by Bottomley (1997) found that group interventions offer mental health benefits for cancer patients, irrespective of stage of diagnosis or treatment. Some evidence suggested that structured interventions offer more benefit than those of a purely supportive nature.

- The RCT by Derdiarian (1989) found that an individualised, formal intervention providing information and counselling enhanced acquisition of information and satisfaction with information in recently diagnosed male cancer patients.

- The meta-analysis by Devine and Westlake (1995) found that in patients with cancer, psycho-educational care interventions were associated with better psychological outcomes (anxiety, depression and mood), physical outcomes (nausea, vomiting and pain) and also with better knowledge acquisition.

- The RCT conducted with patients with melanoma by Fawzy et al. (1990) found that a six week structured, psychiatric group intervention improved outcomes in terms of affective states and coping style at six weeks follow-up and at six months follow-up.

- The RCT conducted with patients with melanoma by Fawzy et al. (1993) found that a six week, structured, psychiatric group intervention which included health education, was associated with a survival advantage, after adjusting for gender and Breslow thickness.

- The meta-analysis by Meyer and Mark (1995) found that psychosocial interventions have positive effects on emotional adjustment, functional

adjustment and treatment and disease-related symptoms in patients with cancer.

- The systematic review by Newell, Sanson-Fisher and Savolainen (2002) concluded that there is tentative evidence for a beneficial psychosocial effect arising from group therapy, education, counselling and cognitive behavioural therapy for patients with cancer.

- The systematic review by Ross et al. (2002) found that studies reporting on the outcomes of psychosocial interventions for patients with cancer were inconsistent in terms of survival, anxiety and depression.

- The meta-analysis by Sheard and Maguire (1999) found that preventative psychological interventions in cancer patients (predominantly educated women with breast cancer) may have a moderate beneficial effect upon anxiety but not depression.

- The qualitative study by Sollner, Gross and Maislinger (2002) concluded that for patients with melanoma, standard methods of psychotherapy are often not appropriate and that specific, structured methods are required.

- The RCT by Trask et al. (2003) found that a cognitive-behavioural intervention was not found in intention-to-treat analysis to reveal significantly lower distress in patients with melanoma at 2 months or 6 months of follow-up, although differences were noted in anxiety and health-related quality of life.

# EVIDENCE TABLE 2.4

***Does involvement of a psychologist improve patient experience of skin cancer?***

***Does involvement of a psychiatrist improve patient experience of skin cancer?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Barsevick *et al.* 2002) | To determine whether research-based recommendations can be made about the clinical management of depression in patients with cancer. | Systematic review of 36 RCTs, 7 non-randomised studies, 5 pre-and post-test studies and 3 meta-analyses. Four qualitative studies (3 systematic reviews and 1 treatment guideline) also included. | No explicit inclusion criteria. Entire range of depressive symptoms from normal sadness to psychiatric disorder. Children excluded.<br><br>**Review undertaken in the US** | Depressive symptoms. | Psycho-educational interventions reduce depressive symptoms in patients with cancer. Behaviour therapy or counselling alone or in combination with cancer education is beneficial. | Broad question with no clear inclusion criteria. Some studies included that did not have depression as an inclusion criterion. Broad range of interventions with considerable variation between studies even within same type. No information on how the chosen outcome was defined in the included studies. Meaningful interpretation of the reviews' findings very difficult. Unpublished data not sought. No details of how studies were selected. Overlap between included primary studies and meta-analyses/systematic reviews? Validity of methods used to assign levels of evidence? Validity of using "vote counting" by reviewers to synthesise evidence? Lack of information on the characteristics of the individual studies. | 1- |
| (Bottomley 1997) | To examine the effectiveness of | Systematic review of 27 studies | Adults with cancer. Most groups were | Depression, anxiety, coping, | Overall, the reviewed evidence suggests that group interventions offer | No rigorous assessment of validity undertaken. Details of | 1- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | psychosocial interventions in reducing the psychological distress associated with cancer. | (n=2064) ) i.e. studies of group interventions that examined the effects of professionally conducted intervention groups (rather than those of a self-help nature or facilitated by non-professional leaders). | either of people with breast cancer or people with mixed diagnoses. One group had Hodgkin's disease and one group had melanoma.<br><br>**Review undertaken in the UK** | quality of life, self esteem, locus of control. | mental health benefits for cancer patients, no matter at what stage of diagnosis or treatment. Some evidence suggests that structured interventions may offer more benefit than those of a purely supportive nature. | study selection procedure not given.<br><br>Not clear if foreign language articles included. Unpublished material sought but only from 1 database. No hand-searching.<br><br>Inclusion criteria are stated but details of included studies are not clearly presented. No rigorous assessment of validity was undertaken although aspects of study design are discussed for each study. Details of the study selection and data extraction procedure are not presented.<br><br>Without many study details being listed in the review it is difficult to tell how representative the author's summary is of the study results. Authors acknowledge limitations of some of the included studies' designs. | |
| (Derdiarian 1989) | To evaluate the effects of an individualised educational/counselling intervention on patient and spouse needs on satisfaction and coping with cancer. | RCT<br><br>Intervention: (n=30) received individualised formal information, counselling, follow-up care and referral as indicated by informational needs assessment; literature published by the American Cancer Society; information relating to other agencies and when and how to contact them; 1- | 60 recently diagnosed male cancer patients. 1st time diagnosis of non-terminal cancer. Not yet receiving treatment. Mean time since diagnosis: 7 days.<br><br>Includes 32 (53%) melanoma patients.<br><br>**US** | Patient-Informational Needs assessment; Spouse-Informational Needs Assessment. Both measure disease, personal, family and social informational needs on a 10-point rating scale; Patient-Satisfaction; Spouse-Satisfaction 24 item rating scale; 8 items assessed information received on coping. | Repeated measures analysis of variance test indicated that the experimental groups gained more information and were more satisfied with that information when compared with their counterpart control groups. | Is follow-up sufficient?<br><br>Validity of instruments? | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | 2 follow-up telephone calls to check adequacy of information.<br><br>Instruments completed independently at baseline and 5-10 days later<br>Control: (n=30) received routine verbal and written informal information, counselling or follow-up care as requested, or if indicated by the clinic informational needs assessment. | | | | | |
| (Devine & Westlake 1995). | To estimate the effects of psycho-educational care on psychological well-being, physical well-being and cancer-related knowledge in adults with cancer, and also to determine whether some types of psycho-educational care are more effective than others. | Meta-analysis of 116 studies: Experimental, quasi-experimental or pre-post single group study design.<br>Intervention:<br>The main analysis is based on 98 studies (5,326 patients) representing 116 experimental treatment groups: education only (20 groups); education with counselling (20 groups); non-behavioural / non-cognitive counselling only (8 groups); behavioural/ cognitive counselling only | Adults with cancer. Age reported in 83% of studies, average 27-69. 92% studies reported gender of which 18% included women only and 70% had more women than men. 85% studies were conducted in US and 10% in Canada.<br><br>**Review undertaken in the US** | Physical well-being: nausea and vomiting and pain. Psychological well-being: anxiety, depression and mood, knowledge about one's health condition. | **Psychological well-being:**<br>Anxiety (68 studies), 95% of studies showed a positive treatment effect that was statistically-significant.<br><br>Depression (48 studies), 92% of studies showed a positive treatment effect that was statistically-significant.<br><br>Mood (30 studies), 87% of studies showed a positive treatment effect that was statistically-significant.<br><br>**Physical well-being:**<br>Nausea (27 studies), 93% of studies showed a positive treatment effect that was statistically-significant.<br><br>Vomiting (16 studies), 81% of studies showed a positive treatment effect that was statistically-significant.<br><br>Pain (13 studies), 92% of studies showed a positive treatment effect that was statistically-significant. | Thorough search although unclear whether English language only.<br>No details of primary studies.<br>No indication of how papers were selected for review.<br>Authors do not report a method for assessing quality of studies, or how many reviewers assessed quality. | 1- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | (65 groups); and behavioural/ cognitive and non-behavioural / non-cognitive counselling (3 groups). | | | **Knowledge:** (19 studies), 95% of studies showed a positive treatment effect that was statistically-significant. | | |
| (Fawzy *et al.* 1990) | To evaluate the immediate and long-term effects on psychological distress and coping methods of a 6-week, structured, psychiatric group intervention for post surgical patients with malignant melanoma. | RCT<br>Intervention:<br>6-week structured psychiatric group intervention consisting of health education; enhancement of problem-solving skills; stress management and psychological support. | Post-surgical melanoma patients<br>38 patients received intervention cf 28 patients receiving standard care.<br><br>Inclusion criteria:<br>a) Recent diagnosis of Stage I or Stage II; b) medical intervention required only excision of primary tumour and any metastatic node; c) no previous psychiatric treatment d) Age 18 or over; e) Able to read and speak English<br>Exclusion criteria:<br>a) Undergoing immunotherapy, chemotherapy, radiotherapy or receiving medication likely to affect immunological function.<br><br>**US** | Affective states and coping style (measured by Profile Of Mood States instrument and Dealing With Illness-Coping Inventory)<br>Psychological data collected at baseline, 6 weeks (immediately following intervention) and at 6 months. | At 6 weeks, the intervention-group patients exhibited higher vigour ($p < 0.026$) and greater use of active-behavioural coping than controls ($p < 0.0001$). At 6 months' follow-up, the group differences were more pronounced. The intervention-group patients showed significantly lower depression ($p < 0.017$), fatigue ($p < 0.022$), confusion ($p < 0.013$), and total mood disturbance ($p < 0.006$) as well as higher vigour ($p < 0.001$). They were also using significantly more active-behavioural ($p < 0.0001$) and active-cognitive coping ($p < 0.03$) than the controls. | Authors propose that delayed effect due to patients practising new skills over 6 months and the intervention particularly important as it provides patients with valuable coping skills after the intervention has ceased.<br><br>However, systematic review by Bottomley et al. (1997) includes this study and claims to have information that a follow-up programme occurred over the telephone, conducted by a research assistant. Possible that this long-term support may have influenced the results. | 1 - |
| (Fawzy *et al.* 1993) | To report the effects of a psychiatric intervention on disease outcome at 10-year follow-up. | RCT<br>Intervention:<br>6-week structured psychiatric group intervention consisting of health education; enhancement of | Same population as at Fawzy 1990, but excluding stage II patients<br>34 experimental: 34 controls (see comments). | Survival; recurrence. | Differences between the intervention and control groups were not significant for outcome at the 10-year follow-up using single covariates. However, being male and having a greater Breslow depth were predictive of poorer outcome. Analysis of multiple covariates also revealed that sex and Breslow | Subject numbers vary between text and tables and control group seems to have increased over 10 years!<br><br>Validity of stats not assessed.<br><br>Same proviso as above – | 1- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | problem-solving skills; stress management and psychological support. | **US** | | depth were significant for recurrence and survival. In addition, participation in the intervention was significant for survival. After adjusting for sex and Breslow depth, participation in the intervention remained significant for survival. | intervention group may have received additional support. | |
| (Meyer & Mark 1995) | To determine the effectiveness of psychosocial interventions with adult cancer patients | Meta-analysis of RCTs of groups of adult cancer patients<br><br>I: psychosocial, behavioural or psycho-educational intervention<br>C: No psychosocial intervention or an extremely minimal sham procedure<br>Exclusions: Hospice and terminal home care studies | 45 studies, 62 treatment control comparisons<br>Sample characteristics: Where mean age reported, the values clustered around 50 years.<br>55% of studies reporting gender had more than 60% female.<br>Total sample size not given<br><br>**Review undertaken in the US** | Emotional adjustment<br>Functional adjustment<br>Treatment or disease-related symptoms; clinical measures. | Effect sizes were homogeneous for all 5 categories of dependent measure<br><br>Average effect sizes: Psychosocial interventions have positive effects on emotional adjustment, functional adjustment and treatment and disease-related symptoms. No significant effect seen for clinical outcomes (but numbers small).<br>Emotional adjustment: d= 0.24 (CI, 0.17-3.2)<br>Functional adjustment: d = 0.19 (CI, 0.06-3.2<br>Treatment and disease-related symptoms: d=0.26 (CI,0.16-3.7)<br>Clinical: d=0.28 (CI -0.10-0.44). | | 1+ |
| (Newell *et al.* 2002) | To identify areas where consistent evidence exists regarding the effectiveness of psychological therapies at reducing cancer patients' morbidity and mortality. | Systematic review of RCTs. | No explicit inclusion criteria<br>Heterogeneous cancer patients.<br><br>**Review undertaken in Australia** | Interventions targeted patient anxiety; depression; general or overall effect; hostility, stress or distress, functional ability or quality of life; coping or control skills; vocational or domestic adjustment; interpersonal or social relationships; sexual or marital relationships; nausea; vomiting, pain, fatigue, physical symptoms, conditioned | 627 papers originally identified reporting on 329 intervention trials. However, methodological quality was deemed generally sub-optimal, with only 1 trial achieving a quality rating of "good" and 24 "fair".<br><br>Findings are as follows:<br>There is tentative evidence for a beneficial psychosocial effect arising from group therapy, education, counselling and cognitive behavioural therapy, all of which are believed to operate in the medium to long term. | Review only able to make recommendations for future research other than tentative recommendations.<br><br>Very broad question with broad inclusion criteria.<br>Good details of search strategy but limited to English only publications<br>Unpublished data sought.<br><br>Broad range of interventions with considerable variation between studies even within same type.<br><br>Good details of how studies were selected/ quality assured. | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | nausea, conditioned vomiting, survival and immune outcomes. | | Systematic review checklist not completed as results inconclusive. | |
| (Ross *et al.* 2002) | To evaluate the scientific evidence for an effect of psychosocial intervention on survival from cancer and well-being and in particular on anxiety and depression. | Systematic review of 43 RCTs. | Homogeneous cancer group. Unclear total number of patients considered.<br><br>**Review undertaken in Denmark** | Survival, anxiety and depression and other psychological components of well-being. | 4 of the 8 studies in which survival was assessed showed a significant effect, and the effect on anxiety and depression was also inconsistent, indicating three possible explanations: (i) only some of the intervention strategies affect prognosis and/or well-being and in only certain patient groups; (ii) the effect was weak, so that inconsistent results were found in the generally small study populations; or (iii) the effect was diluted by the inclusion of unselected patient groups rather than being restricted to patients in need of psychosocial support. | Broad question - Psychosocial interventions – diverse.<br>Effects on survival and well-being (broad)<br>Identification of studies: Only 2 databases (not Cochrane), minimal search strategy, manual searches done<br>Not clear whether limited to English studies, by year or whether unpublished literature sought.<br>Significantly, there was no description as to how study quality was assessed and taken into account, although 2 studies were excluded.<br>Not clear how many reviewers were involved at each stage. | 1- |
| (Sheard & Maguire 1999) | To conduct 2 meta-analyses of trials of psychological interventions in patients with cancer, the first using anxiety and the second depression as a main outcome measure. | Meta-analysis of 19 studies (anxiety) and 20 studies (depression). 14 studies were common to the 2 meta-analyses. | Cancer patients, generally skewed towards white, well – educated women with a diagnosis of breast cancer.<br><br>**Review undertaken in the UK** | Anxiety and/or depression, using variety of different measures. | Findings suggest that preventative psychological interventions in cancer patients may have a moderate clinical effect upon anxiety but not depression. There are indications that interventions targeted at those at risk of, or suffering from, significant psychological distress have strong clinical effects. | Only English language. The decisions on whether to include studies not described. Data extraction not described. Summary estimate of effect across studies used. As considerable heterogeneity, random effects model used and several sensitivity analyses performed. Sensitivity analyses also used to address publication bias. **Questionable whether high degree of heterogeneity justified pooling of effect sizes.** | 1+ |
| (Sollner *et al.* 2002) | To determine the kind of psychotherapy useful in skin cancer patients and how psychotherapeutic interventions should be designed. | Qualitative content analysis of records kept of treatment plans and discussions of psychotherapeutic | Crisis intervention, focal therapy and longer-lasting psycho-dynamically orientated psychotherapy | Description of types of interventions; modification of techniques. | Standard methods of psychotherapy are often not appropriate for the confrontation of tumour-related fears in melanoma patients. Modifications of psychotherapeutic interventions and more structured support are necessary | Psychotherapists treating skin cancer patients should receive special education in such methods. To better cope with distressing emotions and to avoid burn-out and withdrawal | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | interventions for individual patients in weekly supervisory sessions. Illustrated using case vignettes. | within a consultation liaison service within a dermatology department of a University Hospital Precise patient details not given.<br><br>**Austria** | | to meet overwhelming negative emotions caused by the existential threat of the disease. Expressive-supportive methods were used combining psychodynamic psychotherapy with relaxation, imaginative methods, and structured picture drawing. | from severely ill or dying patients, psychotherapists should take part in peer supervision regularly. | |
| (Trask *et al.* 2003) | To determine the effect of a cognitive-behavioural intervention on distress and health-related quality of life (HRQOL) in patients with melanoma who had medium-to-high distress. | RCT. | 48 patients who had Global Severity Index scores >or = 60 2 months after their initial visit to the multidisciplinary melanoma clinic. Randomised to receive either standard care or 4 sessions of a cognitive-behavioural intervention (CBI).<br><br>**USA** | Brief Symptom Inventory, the Medical Outcomes Survey Short Form-36, and the State-Trait Anxiety Inventory administered at baseline, at 2 months, and at 6 months. | An intent-to-treat analysis did not reveal significantly lower distress in the CBI group at 2 months or 6 months of follow-up, although differences were noted in anxiety and health-related quality of life (HRQOL). An effect-of-intervention analysis did reveal lower levels of distress in the CBI group at 2 months, with differences approaching significance at 6 months. | Sample size too small to detect effect? (No power calculations). | 1- |

# Patient satisfaction questionnaires

### The question

*Does the use of questionnaires to measure patient satisfaction improve service provision?*

### The nature of the evidence

Three studies were identified as follows:

- One observational study of fair quality.
- Two expert reviews, one of fair quality and one of poor quality.

One review originates from the UK. One study is from Holland and one review was undertaken jointly in the UK and Holland.

One study is of patients with cancer, one review discusses surgeons and one review applies to people who use health services.

### Summary of the supporting evidence for the recommendations

**There is a small amount of low quality evidence on the usefulness of questionnaires to measure patients' satisfaction with care. Evidence from one observational study and one expert review suggests that a response bias can operate whereby patients who respond to questionnaires have less severe illness or greater satisfaction with care than those who do not respond. Studies suggest that questionnaires should be rigorously designed, with strong validity and that when this condition is met their findings can help to evaluate and improve services.**

- The cross sectional survey by Bredart et al. (2001) found that patients with cancer who returned a satisfaction questionnaire were significantly younger, had significantly shorter hospital stay and presented significantly less physical symptoms than non-responders.

- The expert review by Meredith, Emberton and Devlin (1993) argued that when designed rigorously, patient satisfaction questionnaires can help to evaluate service changes and that satisfaction with care should be considered in line with other outcomes such as poor prognosis.

- The expert review by Wensing and Elwyn (2003) concluded that measures of patients' views should be rigorously assessed for validity and that non-responders to questionnaires are more likely to be ill, less satisfied with care provided or less frequent users of healthcare, than responders.

# EVIDENCE TABLE 2.5

## *Does the use of questionnaires to measure patient satisfaction improve service provision?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bredart *et al.* 2001) | To evaluate the feasibility of conducting a patient satisfaction survey in the oncology hospital setting using a questionnaire completed at home 2 weeks after discharge. To assess whether measures of quality of life and demographic and socioeconomic factors are associated with satisfaction. | Cross sectional survey (quantitative): EORTC questionnaire administered before discharge and Comprehensive Assessment of Satisfaction with Care (CASC) questionnaire completed at home 2 weeks after discharge. | Cancer patients treated at a single hospital: predominantly patients with breast cancer or lung cancer. 120 patients completed EORTC and 97 patients completed CASC. 62% of respondents were female.<br><br>**Holland** | Patient satisfaction, quality of life, demographic and socioeconomic characteristics. | Patients who returned the CASC were significantly younger, had significantly shorter hospital stay and presented significantly less problems with physical role and functioning, nausea, vomiting and loss of appetite than non-responders. The CASC found that a higher proportion of patients reported wanting improvement in aspects of care in terms of doctors' provision of information (20%), information on resources for help (19%) and information on medical tests (19%). A higher global score for quality of life predicted higher satisfaction with all aspects of care and longer hospital stay predicted higher satisfaction with medical and nursing care. Author concludes that this study demonstrates the need to enhance patients' information and education regarding care at home, before discharge. | EORTC QLQ-30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire. CASC: Comprehensive Assessment of Satisfaction with Care. Both questionnaires use quantitative scales. Demographic and socioeconomic data collected from medical records. Author notes small size of sample relative to large number of potential predictors evaluated limits the implication of the results. Probable bias due to over representation of patients who are in better physical condition. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Meredith *et al.* 1993) | To report on the implications of patient satisfaction questionnaires on the role of surgeons. | Expert Review (9 references). | Surgeons, and surgical patients.<br><br>**UK** | | Key points:<br>• Political initiatives have urged clinicians to record and respond to patients' experiences of care.<br>• Outpatient consultations are insufficient to discover the real views of patients.<br>• Provision of information to patients in an individually understandable manner is a prerequisite for informed consent.<br>• Patient satisfaction questionnaires should have validity inherent in their design, by question selection, phrasing and scaling. Invalid questionnaires allow misrepresentation and may over estimate patient satisfaction. A valid questionnaire should address as many dimensions of care as possible.<br>• When designed rigorously, patient satisfaction questionnaires can help to evaluate service changes, and can influence the sometimes divergent goals of doctors and managers.<br>• Satisfaction with care should be considered in line with outcomes such as poor prognosis, or receiving bad news. Findings should be used with objectively recordable measures. | Editorial is driven from the surgeon's perspective. | 4 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Wensing & Elwyn 2003) | To examine the use of patient questionnaires, focus groups and surveys and their validity, effectiveness and implementation. | Expert review (26 References cited). | Users of healthcare services.<br><br>**UK / Holland** | | Author argues that:<br>• Increased participation of patients and the public in healthcare is desirable.<br>• Patients contribute to healthcare by providing preferences, evaluations or factual reports.<br>• Measures of patients' views should be rigorously assessed for validity.<br>• Methods to include patients' views must be shown to affect the process / outcome of healthcare, including possible negative effects.<br>• Non responders to questionnaires are more likely to be ill, less satisfied with care provided or less frequent users of healthcare, than responders.<br>• Methods to use patients' views should be shown to be effective, ideally by randomised trials, using original objectives as outcome measures.<br>• It is an ethical and legal rule that patients are involved in their healthcare.<br>• Patient involvement can improve process and outcomes in terms of better implementation of guidelines, improve safety and increase patient satisfaction. | | 4 |

# Patients with skin cancer in clinical trials

### The question

*Are better outcomes achieved for patients with skin cancer through participation in clinical trials?*

### The nature of the evidence

The extent to which children and adolescents with melanoma have access to clinical trials is addressed in Chapter Five, ‘Management of special groups of patients with skin cancer’. For the question set above, five studies were identified as follows:

- Two systematic reviews; one of good quality and one of poor quality, which predominantly included cohort studies
- One literature review of good quality
- Two audits of good quality.

Two reviews were undertaken in the UK and one review was undertaken in the US and the UK. The primary studies are from many different countries and applicability to the UK is therefore limited. The two audits originate from the UK.

All five studies address patients in clinical trials, of which one is directly of skin cancer patients.

### Summary of the supporting evidence for the recommendations

**The studies identified do not reach a clear consensus on whether better outcomes for patients arise through participation in clinical trials. The best quality systematic review found little evidence for better outcomes through participation in trials aside from those arising from the effects of treatments compared, or due to differences between participants and non participants. The same review found no evidence of greater risk arising from trial participation. A previous systematic review concluded that it is likely that clinical trials can have a positive effect on survival and morbidity outcomes, due to the use of standardized treatment through trial protocols. Audit**

**evidence from the UK suggests that trial participation is less than optimal, and largely focussed within large cancer centres.**

- The systematic review by Vist et al. (2004) found that none of five included RCTs found statistically significant differences in outcomes of patients treated within and outside of RCTs. Included cohort studies were significantly heterogeneous, in which 59 of the 73 studies reported no significant differences. The review concluded that participation in RCTs is not associated with greater risks than receiving the same treatment outside RCTs.

- The literature review by Peppercorn et al. (2004) concluded that there is little evidence that trial participation directly improves outcomes for cancer patients and recommended that recruitment messages should focus on the unquestioned contribution of trials to improving the treatment of future patients.

- The systematic review by Braunholtz, Edwards and Lilford (2001) found that weak evidence suggested that clinical trials have a positive effect on the outcome of patients, due to the effects of organised treatment via treatment protocols.

- The audit of 21 NHS Trusts in England undertaken by Poirier et al. (2004) found evidence that trusts do not have sufficient infrastructure to ensure that patients are offered trial entry.

- The audit of the care of patients with cancer undertaken in England and Wales by the Commission for Health Improvement and the Audit Commission (2001) found that only a small proportion of patients with cancer participated in clinical trials, and that smaller hospitals were less likely to offer participation than larger cancer centres.

# EVIDENCE TABLE 2.6

## *Are better outcomes achieved for patients with skin cancer through participation in clinical trials?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Braunholtz *et al.* 2001) | To assess whether there is evidence that RCTs are systematically beneficial or harmful for patients. | Systematic review. | Patients in clinical trials (various settings)<br><br>14 relevant research articles were identified. 10 articles related to trial effects in cancer therapy, 2 in cardiovascular disease, 1 respiratory disease and 1 postoperative care.<br><br>**Review undertaken in the UK** | Survival (12 studies) and morbidity (3 studies). | The evidence was limited in quality and quantity.<br><br>Statistical meta-analysis was not conducted for reasons of heterogeneity and study quality. Weak evidence suggested that clinical trials have a positive effect on the outcome of patients. Sub-group analysis suggested that the "protocol effect" was an important part of this process. The results could also be explained if clinicians who tended to recruit to trials were also better clinicians.<br><br>Authors' conclusions:<br>While the evidence is not conclusive, it is more likely that clinical trials have a positive, rather than a negative effect on the outcomes of patients. Carefully researched treatment protocols should be used for all patients, not just those in trials. | Analysis included in HTA: Edwards, S. J., Lilford, R. J., Braunholtz, D. A., Jackson, J. C., Hewison, J., and Thornton, J. 2001, "Ethical issues in the design and conduct of RCTs.", Health Technology Assessment (Winchester, England), vol. 2, no. 15, pp. 1-132. | 1 - |
| (Peppercorn *et al.* 2004) | To compare outcomes between trial participants and patients treated off protocol. | Literature review of 24 studies which compared outcomes between trial and non-trial patients. A conceptual framework was created to assess the studies. | Numerous populations of patients with different cancer types, including studies of children (which were over represented).<br><br>**Review undertaken** | The review reports on study inclusion criteria, study characteristics, control of baseline imbalances and trial effects. | 14 out of 26 comparisons provided some evidence that patients who enrol in trials have improved outcomes. Children were one of three groups disproportionately represented in positive studies. However strategies to control for confounding factors were frequently inadequate and the review found little generalisable evidence to support the contention that trial | No meta analyses carried out due to concerns with biases in the primary studies. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | **in the UK/US** | | participation directly improves outcomes for cancer patients and recommends that recruitment messages should focus on the unquestioned contribution of trials to improving the treatment of future patients. | | |
| (Vist *et al.* 2004) | To assess the effects of patient participation in RCTs ('trial effects") independent of both the effects of the clinical treatments being compared, and any differences between patients who participated and those who did not. | Systematic review. | Review included 5 randomised studies (patients were randomised to be invited to participate in an RCT or not) and 50 non-randomised cohort studies. Included a total of 31,140 patients treated in RCTs and 20380 treated outside RCTs. Review included comparisons of the following interventions: surgery (27), drugs (22), radiotherapy (14), counselling (8), usual care (9) and active monitoring (8). Clinical specialties of the included studies: oncology (28), cardiology (13), obstetrics and gynaecology (15), psychology (9) and paediatrics (8).<br><br>**Review undertaken in the UK** | Mortality, morbidity and clinically important changes in outcomes measured on continuous scales (such as pain and complication rates). | Randomised studies: None of these 5 studies found statistically significant differences in outcomes of patients treated within and outside of RCTs. Quantitative synthesis was not conducted because of heterogeneity in research design. Cohort studies: There was statistically significant heterogeneity among the 73 dichotomous outcome comparisons ($p < 0.01$, $I2=89.0\%$). In 59 of the 73 comparisons reported, no significant differences in outcomes were found. 10 comparisons reported statistically significant better outcomes for patients treated within RCTs, and four comparisons reported statistically significant worse outcomes for patients treated within RCTs. Sub group analyses were carried out for different types of treatment (surgery, chemotherapy, etc.), for different clinical areas (oncology, cardiology, etc.) and for the different reasons patients refused to participate in the RCT (treatment preference etc.). None of these sub group analyses helped explain the heterogeneity in the overall analysis. (Statistical results of subgroup analyses were not included in the review). Authors' conclusions: This review indicates that participation in RCTs is not associated with greater risks than receiving the same treatment outside RCTs. These results challenge the assertion that the results of RCTs are not applicable to usual practice. | | 1++ |
| (Poirier *et al.* 2004) | To gain a baseline of skin cancer MDT activity in the South West Region, and to compare this against the Manual of | Audit of activity against local standard, using questionnaire based on the local | 21 NHS Trusts in England – representing patients with skin cancer. | Adherence to standard. | **Summary points:**<br>• A total of 5 out of 11 Trusts knew whether they had a list of agreed trials for their cancer network. This suggested that many trusts do not | | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | Cancer Standards.<br><br>To share best practice across the region. | standard. Data were obtained between December 2003 and February 2004. | **UK** | | yet have the infrastructure within which to ensure patients are offered trial entry. | | |
| (Commission for health improvement & Audit Commission 2001) | To document the experiences of people with cancer and the complexities of the multiple services with which they come into contact, in the light of recommendations made in the Calman-Hine Report (1995). | Major audit undertaken by the Commission for Health Improvement (CHI) and the Audit Commission. | People with cancer in England and Wales.<br><br>**UK** | Extent of implementation of recommendations made in the Calman-Hine Report (1995). | **Findings:**<br>• Only a small proportion of patients with cancer are involved in clinical trials.<br>• Cancer centres can be involved with 50 or 60 different trials, whereas smaller hospitals usually take part in only a few.<br>• Many consultants outside centres argue that they are too pressed providing a basic service to be able to give time to trials. | | 3 ++ |

# Protocol based care

### The question

*Does the use of protocols provide better outcomes for patients with skin cancer?*

### The nature of the evidence

Two expert reviews of good quality were identified, one of which was produced in part by NICE. No high level evidence was identified. Both sources originate from the UK and applicability to the UK is high.

### Summary of the supporting evidence for the recommendations

**There is expert review evidence that supports the use of protocols in delivering NHS services. Protocols are described as local arrangements to implement national guidelines and are cited as improving the quality of services through using practices that are based on evidence. Cited benefits include improved patient outcomes, cost effectiveness and reduction in variation of practice.**

- The policy information resource produced by the NHS Modernisation Agency and NICE (2005) describes protocols as the detailed descriptions of the steps taken to deliver care, designed locally to implement National Standards (which are synonymous with 'integrated care pathways'). The authors conclude that the use of protocols promotes the use of safe, high-quality, clinically effective treatments, increases cost effectiveness and multidisciplinary team working and reduces variation in quality of service.

- The education and debate article by Cambell et al. (1998) describes integrated care pathways as care plans that detail the essential steps in the care of patients with a specific clinical problem and which aim to facilitate the introduction into clinical practice of clinical guidelines. Cambell et al. (1998) cite potential benefits (including improved patient outcomes and patient satisfaction) and concerns (including undermining clinical judgement) associated with integrated care pathways.

# EVIDENCE TABLE 2.7

## *Does the use of protocols provide better outcomes for patients with skin cancer?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Cambell *et al.* 1998) | To describe integrated care pathways (ICPs) and provide advice on how to create and use them and review the evidence on their effectiveness. | Expert literature review (education and debate article): Search utilised Medline, the National Pathways Users' Group, and King's Fund library databases. | NHS patients: largely secondary/tertiary care patients.<br><br>**UK** | Summarises the evidence on integrated care pathways, denoting: Aims, examples of use, developmental steps, benefits, concerns and barriers to implementation. | **Summary points**<br>• Integrated care pathways are care plans that detail the essential steps in the care of patients with a specific clinical problem and describe the expected progress of the patient.<br>• They exist for over 45 conditions or procedures, and national users' groups exist to give advice and support in their use.<br>• They aim to facilitate the introduction into clinical practice of clinical guidelines and systematic, continuing audit into clinical practice: they can provide a link between the establishment of clinical guidelines and their use.<br>• They help in communication with patients by giving them access to a clearly written summary of their expected care plan and progress over time.<br>**Benefits of ICPs**<br>• Reduction in the length of stay in hospital.<br>• Reduction of costs of patient care,<br>• Improved patient outcomes (improved quality of life, reduced complications).<br>• Increased patient satisfaction with the service.<br>**Concerns about ICPs**<br>• Investment of time which could be | Many examples of use are not cancer specific.<br><br>**Relationship with *protocols:*** Details of care from an agreed integrated pathway are set out in local protocols.<br><br>Authors conclude that strategies which involve staff developing their own guidelines and incorporate an implementation plan which is closely related to clinical decision making, are more likely to be adopted and to change clinical practice. ICPs do not exclude decisions based upon clinical judgement but variance from agreed ICPs/protocols should be justified and documented. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | spent in other clinical activities.<br>• May discourage appropriate clinical judgment being applied to individual cases. | | |
| (NHS Modernisation Agency & National Institute of Clinical Excellence 2005) | To provide information to support the development of protocol-based care in England. | NHS information leaflet (available online). | NHS patients.<br><br>**UK** | Provides overview of protocol-based care and describes the policy setting in which it operates. | This leaflet describes protocol based care as follows:<br>• Local protocols are the detailed descriptions of the steps taken to deliver care, designed locally to implement National Standards and to utilise the best available evidence where no National Standard exists [protocols are synonymous with 'integrated care pathways'].<br>• Protocols are developed on a multi disciplinary basis, reflecting local services and staffing arrangements.<br>• Protocol-based care promotes the use of safe, high – quality, clinically effective treatments.<br>• Protocol-based care provides clear statements and standards for the delivery of care locally.<br>• Protocol-based care helps reduce unacceptable variations in quality.<br>• Protocol-based care can be used to help implement the clinical standards of NICE and National Service Frameworks.<br>• Protocol-based care helps provide assurances that good practice is being followed.<br>• Protocol-based care provides a source of information and promotes high quality record keeping.<br>• Healthcare professionals have long recognised the value of protocols as tools to ensure clinical effectiveness, cost effectiveness, safety and consistency of care and coordination of services. It also provides a framework for working in multi disciplinary teams. | No references provided. Interpreted as high-level policy information resource. Graded as 'expert opinion'. | 4 ++ |

# Palliative and supportive care

### The question

*What are the specific issues for patients with skin cancer for palliative and supportive care?*

### The nature of the evidence

Six studies were identified as follows:

- One systematic review of poor quality.
- Three observational studies of fair quality.
- Two sets of clinical guidelines of good quality.

Three studies originate from the UK, one study is from Australia and one study each is from Iceland and Austria. Generalisability to the UK is limited.

Five studies relate to patients with melanoma. One study is of patients with skin cancer and the systematic review is of patients with advanced cancer.

### Summary of the supporting evidence for the recommendations

**Systematic review evidence supports a multidisciplinary approach to palliative care, suggesting that specialist teams in palliative care improve patient satisfaction and meet more patient and family needs than conventional care. The same evidence suggests that multidisciplinary approaches to palliative care reduce the overall cost of care by reducing the amount of time patients spend in acute hospital settings. Evidence from observational studies suggests that positive attitudes from staff of all disciplines can help patients undergoing palliative treatment and also highlights the need for peer support. In patients undergoing palliative treatment for melanoma there is evidence for deterioration in mood and ability to function and also difficulty in communicating palliative treatment issues with staff. Cross sectional evidence suggests that in patients with stage IV melanoma, individual coping and psychological adjustment to disease are closely related to changes in quality**

**of life. Evidence based guidelines produced by panels of experts in the UK support the role of specialist palliative care teams in the treatment of patients with melanoma.**

- The longitudinal study by Brown et al. (2000) studied patients with terminal stage IV melanoma during the last year of life and found that while patients work hard to actively cope with their disease, they experience increasing levels of tiredness, and deterioration in their mood and ability to function in their daily lives. Cognitive appraisal, coping style and quality of life indicators were associated with psychological adjustment.

- The systematic review by Hearn and Higginson (1998) found that specialist teams in palliative care improve satisfaction and identify and deal with more patient and family needs than conventional care. Multidisciplinary approaches to palliative care reduce the overall cost of care by reducing the amount of time patients spend in acute hospital settings. Teams involving a nurse specialist, general practitioner and a district nurse provided the best services for those patients requiring symptom relief.

- The cross sectional study by Sigurdardottir et al. (1995) explored attitudes towards palliative chemotherapy and quality of life in patients with metastatic melanoma and found that 50% of patients reported treatment troublesome whereas 50% of patients felt that it had been helpful and very few had thought about stopping. Patients communicated primarily with family about treatment toxicity, leaving nurses with insufficient information to assess effects on an individual level. In the care of patients with metastatic melanoma the professional's positive view increased patient enthusiasm for chemotherapy, irrespective of discipline.

- The qualitative study by Sollner et al. (2002) concluded that psychotherapists treating skin cancer patients should receive regular peer support to avoid 'burn out' or withdrawal from terminally ill patients.

- Guidelines of the British Association of Dermatologists (BAD, 2002) recommend that patients with melanoma should have access to a palliative

care team providing expertise in symptom control and psychosocial support, and that links should be made with community cancer support networks.

- Guidelines of the Scottish Intercollegiate Guidelines Network (SIGN, 2003) recommend that patients with advanced melanoma require a coordinated, multidisciplinary approach with input from a palliative care team and that patients with poorly controlled symptoms should be referred to specialist palliative care at any point in their cancer journey.

# EVIDENCE TABLE 2.8

## *What are the specific issues for patients with skin cancer for palliative and supportive care?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Brown *et al.* 2000) | To consider patterns of change in cognitive appraisal, coping and psychological adjustment during the last year of life and to consider covariates associated with patients' psychological adjustment. | Longitudinal observational study. | 110 patients with melanoma completing at least one questionnaire in the last year of life.<br><br>**Australia** | Repeated measures linear regression was used to model cognitive appraisal, coping and psychological adjustment. | Patients' cognitive appraisal of their disease remained relatively stable, whereas use of active coping strategies increased. Some deterioration in psychological adjustment, particularly in patients' ability to minimise impact of disease on daily life, but significance was lost when patients' level of tiredness was included in the model. Cognitive appraisal, coping style and quality of life indicators were all associated with psychological adjustment. | Authors conclude that while patients work hard to actively cope with their disease, they experience increasing levels of tiredness and deterioration in their mood and ability to function in their daily lives.<br><br>Participation rate low – questions about generalisability. Timing and spacing of questionnaires means that subtle end-of-life changes could have been missed.<br><br>Data collected longitudinally but associations between psychological adjustment and the covariates are cross-sectional and causality cannot be implied.<br><br>Findings suggest that while patients work hard to actively cope with their disease, they experience increasing levels of tiredness, and deterioration in their mood and ability to function in their daily lives. | 3 |
| (Hearn & Higginson 1998) | To determine whether teams providing specialist palliative care improve | Systematic review of RCTs, comparative and | Any patient with advanced cancer and their families. | Aspects of symptom control. Patient and carer | Four out of five RCTs and the majority of comparative studies indicated that the specialist, co-ordinated approach | Some studies from US – different healthcare system. | 1- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | the health outcomes of patients with advanced cancer and their families or carers when compared with conventional services. | observational studies (18 relevant studies identified).<br><br>Inclusion criteria: Studies which considered the use of specialist multi-professional teams (MPT) caring for advanced cancer patients and their families. Excluded studies which focused on one cancer site to avoid problems with generalisability Results not combined. | Specific cancers not described. Information about age and gender not available for all studies.<br><br>Intervention: Diagnosis, treatment, management by MDTs.<br><br>**UK** | satisfaction. Healthcare utilisation and cost. Place of death. Psychosocial indices. Quality of life. | resulted in similar or improved outcomes. Results support use of specialist MDTs in primary care to improve satisfaction of patients with advanced cancer and their family. Evidence suggests MDTs were more able to identify and deal with patient/family needs, and provided access to other services. Teams involving a nurse specialist, GP and a district nurse provided the best services for those patients requiring symptom relief.<br><br>Some studies reported cost information. Results showed a tendency for reduced or equal costs in the intervention group, with reduction in number of inpatient hospital days. Formal analysis not conducted. | Comprehensive search strategy. Hand-searching. Attempts to find unpublished material. All languages considered.<br><br>Validity of primary studies evaluated with grading system. Appropriateness of various outcome measures considered when allocating grade. However, how this was implemented not discussed and results and conclusions did not take them into account. Conclusions may overstep the quality of the data in the included studies. | |
| (Roberts *et al.* 2002) | To provide evidence based recommendations on behalf of the British Association of Dermatologists for the treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma. | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | Recommends:<br><br>All patients should have access to a palliative care team providing expertise in symptom control and psychosocial support. Links should be made with community cancer support networks as soon as possible. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma. | Recommendations for practice. | Patients with advanced melanoma require a coordinated multidisciplinary approach with input from a palliative care team.<br><br>Patients with poorly controlled symptoms should be referred to specialist palliative care at any point in their cancer journey. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |
| (Sigurdardottir *et al.* 1995) | To provide a broad picture about attitudes | Cross-sectional observational study | All patients, their next-of-kin and staff | QOL measures and questions | After 2-3 months of therapy half the patients reported treatment | Authors conclude that the assumption can be made that | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | towards chemotherapy for palliation of metastatic melanoma. | as part of a longitudinal QOL study conducted in connection with a clinical trial of combination chemotherapy. | on a Melanoma Unit.<br><br>**Iceland** | concerning value of treatment; communication about treatment toxicity. | troublesome, 50% felt it had been helpful and very few had thought about stopping. Patients communicated mainly with family about treatment toxicity, leaving nurses with insufficient information to assess effects on an individual level. Staff (irrespective of discipline) had an overwhelmingly positive attitude to chemotherapy and found satisfaction in their work. Work provided motivation and a feeling of being needed by patients. | the professional's positive view increases patient enthusiasm for chemotherapy.<br><br>Issues for professional ethical debate around continuing treatment raised.<br><br>Authors suggest that it seems reasonable to assume that the professional's view increases the patient's enthusiasm for chemotherapy. | |
| (Sollner *et al.* 2002) | To determine the kind of psychotherapy useful in skin cancer patients and how psychotherapeutic interventions should be designed. | Qualitative content analysis of records kept of treatment plans and discussions of psychotherapeutic interventions for individual patients in weekly supervisory sessions. Illustrated using case vignettes. | Crisis intervention, focal therapy and longer-lasting psycho dynamically orientated psychotherapy within a consultation liaison service within a dermatology department of a University Hospital Precise patient details not given.<br><br>**Austria** | Description of types of interventions; modification of techniques. | Standard methods of psychotherapy are often not appropriate for the confrontation of tumour-related fears in melanoma patients. Modifications of psychotherapeutic interventions and more structured support are necessary to meet overwhelming negative emotions caused by the existential threat of the disease. Expressive-supportive methods were used combining psychodynamic psychotherapy with relaxation, imaginative methods, and structured picture drawing. | Psychotherapists treating skin cancer patients should receive special education in such methods. To better cope with distressing emotions and to avoid burn-out and withdrawal from severely ill or dying patients, psychotherapists should take part in peer supervision regularly. | 3 |

# EVIDENCE TABLE 2.9

## Results of the Skin Cancer Guideline Development Group survey

*Note – A full report is included as Appendix B.*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Skin Cancer Guideline Development Group on behalf of NICE 2004) | To measure the experience of patients with skin cancer in the UK. | Postal questionnaire survey. | 94 patients with skin cancer of different types:<br><br>melanoma (55), non-melanoma (24), unclassified (11), missing data (4).<br><br>Age range reported categorically – the majority of patients were aged between 30 and 70 years. | Patients reported experience of diagnosis, referral, treatment and follow-up and their reported associated emotions. Patients' reported need for information and support. | **Quantitative results**<br>• 37/91 patients sought advice from a person other that the GP, including partner, family and friends in the vast majority of cases.<br>• 32/89 patients reported feeling 'worried' when they first thought that something was wrong with their skin.<br>• 30/58 patients reported a delay in being told the diagnosis of skin cancer.<br>• 12/22 patients had their skin cancer treated by their GP and 71/94 were referred to hospital for tests and treatment by their GP.<br>• The commonest reported needs for information at diagnosis concerned treatment, seriousness of condition, potential for spread, recurrence and risk of mortality.<br>• 66/94 patients reported that there was 'not enough time' with health professionals.<br>• 78/91 patients thought that the amount of information provided on their diagnosis was 'about right'.<br>• 68/78 of patients understood everything about their diagnosis.<br>• 49/80 patients were given written information at diagnosis.<br>• 53/90 patients were invited to bring a relative to appointments for support.<br>• The commonest treatments | Data missing for a proportion of patients for many outcomes, therefore denominators in proportions are based upon patients for whom data are available in each case. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | received were surgery, excision and chemotherapy / radiotherapy.<br>• 44/56 patients were not offered make-up to conceal scars after treatment, whereas 15/44 patients would have liked this.<br>• 66/80 patients did not report special needs during their treatment. Of those who reported needs, needs were met in 12/14 of patients.<br>• 61/75 of patients did not have any difficulty in accessing services for skin cancer.<br>• The most commonly reported professionals that patients wanted to see at appointments were consultants, doctors and nurses.<br>• 71/82 patients were being followed up at the time of study, most commonly by hospital doctors.<br>• 56/85 patients were happy to perform self examination for skin cancer.<br>• 63/87 patients thought that skin cancer had affected their life, most commonly in terms of sun awareness.<br>• 79/90 patients thought that health professionals respected what patients had to say.<br>• 47/75 patients thought that skin cancer services could be improved. | | |

# Chapter 3 – Organisation of skin Cancer Services

## Introduction

### Existing NICE guidelines

The Clinical Guidelines issued by NICE, *Referral Guidelines for Suspected Cancer* make recommendations for referral of patients with suspected cancer from primary care to specialist services. The referral guidelines recommend that patients presenting with skin lesions suggestive of skin cancer or in whom a biopsy has been confirmed should be referred to a team specialising in skin cancer. The referral guidelines make specific recommendations for appropriate accredited training of primary healthcare professionals, and also for referral of patients with melanoma, SCC and BCC.

### Audit data from stakeholders

During the first consultation period in the development of this guidance, a number of registered stakeholders from nine NHS Trusts in England provided audit data on current primary care activity with regard to skin cancer. The data provided evidence of the proportion of skin tumours that are currently managed in primary and secondary care, and are shown in Appendix D. This data demonstrated that the proportion of skin cancer tumours managed in primary care had a range of 1.2% to 17%. The audits found that between 1.4% and 13% of melanoma tumours are managed in primary care. This proportion for SCC had a range of 0.7% and 10% and for BCC had a range of 1.3% to 8.8%.

## The role of General Practitioners in the diagnosis and treatment of skin cancer

### Melanoma

#### The question

*In patients with pigmented skin lesions, do General Practitioners (GP), General Practitioners with a Special Interest in Dermatology (GPSI) or Dermatologists provide the most accurate diagnosis?*

#### The nature of the evidence

22 studies were identified as follows:

- Five RCTs, two of good quality and two of poor quality
- One systematic review of good quality, but including non randomised studies
- Fourteen observational studies, nine of fair quality and one of good quality.
- Two clinical guidelines, of good quality.

Eight studies originate from the UK. Four studies are from the US and three studies are from Australia. The remaining seven studies are from Western Europe (Belgium, Italy, Denmark, Sweden and Ireland).

Six studies compare diagnostic accuracy between dermatologists or specialists with that of GPs. One study is of clinicians at a specialist pigmented lesion clinic, two studies are of dermatologists alone and two studies are of GPs alone.

**Summary of the supporting evidence for the recommendations**

**Two RCTs demonstrated that provision of training to GPs significantly improved their ability to diagnose melanoma and correctly manage patients accordingly. In one trial the training was delivered via the internet.**

**Two RCTs examined the use of a diagnostic algorithm and camera as diagnostic tools for primary care physicians treating patients with pigmented lesions, suspicious of melanoma. One trial demonstrated a reduction in the proportion of excised lesions that were found by pathology to be benign, whereas the other trial found no effect.**

**One RCT found little evidence that provision to GPs of feedback on their diagnostic and management ability for skin lesions improved their ability. However, provision of feedback was associated with an improvement whereby GPs were more likely to include a clinical diagnosis when submitting a pathology request form.**

**Observational studies generally report high diagnostic accuracy for dermatologists for skin cancer, particularly with regard to differentiation between melanoma and other pigmented lesions. There is no clear consensus amongst observational studies on the ability of GPs to correctly diagnose skin cancer, particularly**

**melanoma. Systematic review evidence reflects this inconsistency since the final conclusion of one review was that the data from primary studies were inadequate to demonstrate differences between dermatologists and GPs in diagnostic and decision making outcomes.**

**There is evidence from observational studies that experience of having worked in dermatology departments is associated with greater diagnostic ability for melanoma by GPs. RCT evidence strongly suggests that training of GPs in the recognition of melanoma can improve their diagnostic accuracy and rate of appropriate referral of patients to specialists. Clinical guidelines produced by the British Association of Dermatologists recommend that patients with lesions suspicious of melanoma should be referred urgently to a dermatologist or surgeon/plastic surgeon with an interest in pigmented lesions, in line with the two week referral standard.**

**There is observational study evidence that skin cancer lesions constitute a small proportion of all skin lesions seen in primary care and that melanoma is rarely seen by GPs. There is audit evidence that in the UK, of all referrals of lesions suspicious of skin cancer made by GPs under the two week referral standard, 12 % are confirmed as malignant and of all confirmed malignancies, only 42 % are referred in accordance with the standard.**

- The randomised controlled ecological study by Del Mar and Green (1995) in which two cities were randomised to either intervention or control found that provision of a diagnostic algorithm and Polaroid camera was associated with a significant reduction in the number of pigmented lesions excised by doctors (predominantly GPs) that were subsequently found to be benign. Significantly fewer doctors in the intervention city than the control city offered exclusion of malignancy as the reason for excision.

- The RCT by English et al. (2003) found that provision to general practitioners in Australia of a diagnostic algorithm and Polaroid camera did not decrease the ratio of benign pigmented skin lesions to melanomas excised by general practitioners.

- The RCT undertaken by Raasch, Hays, and Buettner (2000) found very little effect arising from an intervention whereby GPs in Australia were given feedback on their ability to correctly diagnose and manage malignant and benign skin lesions, since patient factors appeared to heavily confound the study. However the intervention

was associated with a significant improvement in terms of including clinical diagnosis with pathology request forms.

- The RCT by Gerbert et al. (1998) demonstrated that a brief educational intervention improved the ability of primary care physicians to correctly diagnose melanoma and to plan the optimal management of patients with skin cancer, including melanoma.

- The RCT by Gerbert et al. (2002) found that an internet delivered educational intervention on skin cancer diagnosis and planning was associated with a significant improvement in the ability of GPs in overall diagnosis and evaluation planning, diagnosis of melanoma and seborrhoeic keratosis, diagnosis and evaluation planning of SCC and BCC and evaluation planning for actinic keratosis.

- The prospective study of dermatologists and primary care physicians in Belgium by Brochez et al. (2001) found that recognition of melanoma was proportional to melanoma exposure in everyday practice and that dermatologists correctly diagnosed a higher proportion of pigmented lesions than GPs. After a lecture on melanoma, sensitivity of GPs to recognise malignant disease significantly increased, without a significant decrease in specificity.

- The non-randomised intervention study by Carli et al. (2005) found that primary care physicians in Italy were able to correctly diagnose 46.8% of melanoma tumours at baseline, although 96.1% of melanoma observations were correctly referred to a dermatologist. A 4 hour formal training session increased the specificity of family doctors with regard to correctly referring suspicious lesions to a dermatologist (i.e. less false-positive referral of benign lesions) without any significant loss in sensitivity in detecting melanoma.

- The observational study by Carli et al. (1998) found that primary care physicians in Italy were able to diagnose 37% of lesions correctly as suspicious due to clinical atypia.

- The systematic review by Chen et al. (2001) found the sensitivity of primary care physicians in diagnosing melanoma to have range 0.42-1.0, and this range for dermatologists was 0.81-1.0. Sensitivity of decision making between performing a biopsy versus making a referral had range 0.70-0.91 for primary care physicians and 0.82-1.0 for dermatologists. Specificity in this context had range 0.51-0.87 for

primary care physicians and 0.70-0.89 for dermatologists. However there was insufficient data from the primary studies to conclude whether GPs or dermatologists were more effective in correctly diagnosing melanoma or making correct biopsy / referral decisions.

- The survey of UK dermatologists undertaken by Cox (2004) found that amongst skin lesion specimens submitted for histology under the two week referral rule, GPs were more likely to suspect melanoma than SCC. The overall proportion of confirmed skin cancers amongst two-week rule referrals was 12%, but only 42% of tumours were referred by this route.

- The prospective observational study by Duff et al. (2001) found that the specialists at a pigmented lesion clinic in the UK had sensitivity 98.5% and specificity of 89.2% for the diagnosis of melanoma and a negative predictive value of 99.9%.

- The audit of histologically confirmed melanoma tumours carried out in the UK by Jackson et al. (2000) found that the clinical diagnosis of malignant melanoma was made in 9% of GP cases and 35% of the hospital specialist cases. However another 45.5% of GP cases and 38% of hospital specialist cases were regarded as suspicious pigmented lesions clinically. The histological diagnosis was of superficial spreading malignant melanoma in 72% of the GP and 69% of the hospital specialist cases. The authors recommended that GPs make recognition of melanoma in the first instance.

- The prospective study of primary care physicians in Denmark by Jemec et al. (1999) found the median diagnostic accuracy (sensitivity) for pigmented lesions was 0.75 (95% CI 0.65-0.80) The specificity was 0.70 (95% CI 0.68-0.79) and the positive predictive value was 0.70 (95% CI 0.62-0.77). The authors concluded that these values were comparable with those published for trainee dermatologists and suggested that ongoing interest is a greater determinant of clinical acumen than is initial training.

- The retrospective study by Lindelof et al. (1998) found that of 47 cases of probable recognisable malignant melanoma, there was insufficient management by dermatologists in 7 (15%) i.e. missed or delayed diagnosis. The authors concluded that clinical detection rate by dermatologists is high.

- The retrospective study in Ireland by Morrison et al. (2001) found that there was agreement between family practitioners and dermatologists on the diagnosis of skin cancer tumours (BCC, SCC and melanoma) in 54% of cases. Histologically proven skin cancers were diagnosed accurately in only 22% of cases by family practitioners, compared to 87% of cases by dermatologists.

- The retrospective study by Morton and Mackie (1998) found diagnostic accuracy with regard to pigmented lesions for 2 dermatologists with > 10 years experience to be 80% (sensitivity 91%, positive predictive value 86%). Diagnostic accuracy for 2 Senior Registrars with 3-5 years experience was 62%. Diagnostic accuracy for 6 Registrars with 1-2 years experience was 56%.

- The retrospective study by Osborne et al. (2003) found that the false negative rate in detecting melanoma of Dermatology clinics was 29% and for GPs it was 54% ($p < 0.0001$). The authors concluded that the false negative rate of melanoma was lower in the pigmented lesion clinic than in other clinics studied (including GPs).

- Clinical guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists recommend that patients with lesions suspicious of melanoma should be referred urgently to a dermatologist or surgeon / plastic surgeon with an interest in pigmented lesions, in line with the two week referral standard.

- Clinical guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that clinicians be familiar with the seven point check list to assist in the diagnosis of melanoma.

- The cross sectional survey by Gerbert et al. (1996) found that dermatologists performed significantly better than primary care physicians in diagnosing 6 categories of lesion (including melanoma) and formulating treatment plans. For primary care physicians, having worked in a dermatology clinic (OR 8.32, 95% CI 1.8-23.2) was associated with higher scores for diagnosis. The primary care physicians' diagnostic error rate was 50% for melanoma and NMSC, compared with 19% for dermatologists.

- The retrospective case series study by Julian (1999) of patients seen at a single practice over a 5 year period found that 74 (3%)had skin cancer. Of the 74 skin

cancer patients, 2 patients had melanoma, which represented 2.7% of skin cancers seen.

- The cross sectional survey of GPs undertaken by Offidani et al. (2002) found that of 288 responding GPs, 262 (91%) correctly identified melanoma.

# EVIDENCE TABLE 3.1

***In patients with pigmented skin lesions, do General Practitioners (GP), General Practitioners with a Special Interest in Dermatology (GPSI) or Dermatologists provide the most accurate diagnosis?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Brochez *et al.* 2001b) | To evaluate diagnostic ability of GPs and dermatologists concerning pigmented skin lesions. To investigate whether diagnostic ability of GPs changed after a lecture on melanoma. | Prospective study. | 160 GPs and 60 dermatologists.<br><br>Slides of 13 pigmented skin lesions.<br><br>**Belgium** | Naked eye diagnostic accuracy; sensitivity, specificity, positive predictive value, likelihood ratio, index of suspicion for melanoma. | GPs correctly evaluated biologic behaviour of Pigmented skin lesions in 72% of the evaluations. In 71% of these evaluations they correctly identified the lesions. Proportion of lesions correctly identified was positively correlated with the frequency of Pigmented skin lesions in everyday practice.<br>Dermatologists made a correct identification of the lesions in 88% of all evaluations, and they correctly evaluated biologic behaviour in 94% of these. Recognition of melanoma was proportional to melanoma exposure in everyday practice. Thick melanomas were better recognised than thin melanomas in both physician groups. After a lecture on melanoma, sensitivity of GPs to recognise malignant disease increased from 72% to 84%, without a significant decrease in specificity. The proportion of lesions correctly identified also rose significantly (66% vs. 52%). | Selection bias - GP population comes from those attending educational courses.<br><br>Small number of test slides to base findings on (e.g. 5 melanomas). | 3 |
| (Carli *et al.* 2005) | To evaluate the impact of a short formal training on diagnostic and referral accuracy of family doctors in melanoma screening. | Before and after intervention study: A formal 4-h training session was given to a sample of 41 practising family doctors. A test of diagnostic ability for pigmented lesions | 41 family doctors.<br><br>**Italy** | Diagnostic sensitivity and specificity of family doctors pre and post educational intervention. | Although only 46.8% of observations yielded a correct melanoma diagnosis at baseline, 96.1% of melanoma observations were correctly associated with intention to refer the lesion to dermatologist. After training, the percentage of correct melanoma diagnosis significantly increased (76.2%, P = 0.01) while no further improvement was found as to | Gold standard was histology from the lesions presented to GPs as photographs. Observers were blind to pre test answers. Post test was immediately after training session. Discussed in UK and Italian context, where GP is the gatekeeper to dermatology services. | 3 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | was made pre and post intervention. | | | sensitivity of referral (94.8%, P = 0.58). Compared to baseline, post-training evaluation showed a significant reduction of benign lesions sent to dermatologist: the percentage lowered from 52.1 to 35.8% (P = 0.0014) for melanocytic nevi and from 38.6 to 17.5% (p < 0..001) for benign non-melanocytic lesions (pigmented seborrhoeic keratoses, dermatofibromas, and vascular lesions). Grouping these two diagnostic categories, the overall specificity in dermatology referral increased from 55.0% at baseline to 73.1% after training (p < 0..001). In conclusion, attendance at a 4-h formal training session was able to increase the specificity of family doctors as to dermatologist referral of suspicious lesions (less false-positive referral of benign lesions) without significant loss in sensitivity concerning melanoma. | | |
| (Carli *et al.* 1998) | To assess the characteristics of pigmented lesions selected by GPs to be submitted to dermatology services. | Prospective observational study. | 262 subjects consecutively observed in two months at the PLC of the Department of Dermatology in Florence.<br><br>**Italy** | Diagnostic accuracy. | 37% of lesions were correctly defined as suspicious by GP because of their clinical atypia (melanoma and atypical nevi, NMSC, clinically equivocal lesions). In the other cases, the subjects presented benign pigmented lesions, both of melanocytic (common nevi, blue nevi) or non melanocytic origin (seborrhoeic keratosis, dermatofibromas, angiokeratoma). | | 3 |
| (Chen *et al.* 2001) | To compare accuracy of dermatologist and primary care physicians in identifying pigmented lesions suggestive of melanoma and making the appropriate management decision to perform a biopsy or to refer the patient to a specialist. | Systematic review.<br><br>32 prospective and retrospective studies. Considered eligible if they reported or contained data to calculate either sensitivity or specificity for either DA or B/R accuracy of either PCPs or dermatologists in relation to melanoma. | 10 prospective studies involved 583 dermatologists and 2366 PCPs assessing between 1-12 mm, 5 of which provided data for both diagnostic and B/R accuracy. 7 prospective studies provided data for both dermatologists and PCPs, 2 studies provided data on PCPs only and 23 on dermatologists only. | Sensitivity, specificity for diagnostic and biopsy or referral accuracy. | **Diagnostic accuracy (DA) - prospective studies only.**<br>The sensitivity of dermatologists ranged from 0.81 to 1.00 (6 studies); No studies reported specificity. The sensitivity of PCPs ranged from 0.42 to 1.00 (9 studies), while the specificity was 0.98 (1 study).<br>*Biopsy/referral (B/R) accuracy - prospective studies only*.<br>The sensitivity of dermatologists ranged from 0.82 to 1.00 (5 studies), while the specificity ranged from 0.70 to 0.89 (3 studies). The sensitivity of PCPs ranged from 0.70 to 0.91 (6 studies), while the specificity ranged from 0.51 to 0.87 (4 studies). | Very broad inclusion criteria for participants and study design – neither physicians nor dermatologists were defined and no minimum standard for study design in terms of the number or range of melanomas assessed (or whether *in vivo* or slides) , and whether both groups of participants were included, or method of diagnosis. Consequently, a large number of the studies included could not be used in the analysis. The authors pointed out potential biases as a consequence of who | 2+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | **US** | | The summary ROC curve for B/R accuracy (based on 3 studies) showed the curves for the two groups crossing, so that there was no or insufficient evidence that one group was better than the other. This result was reported not to be robust on the basis that a shift of 10% in one group's results would have yielded different results.<br><br>All 4 studies that found sensitivities of 1.00 were based on the assessment of one single melanoma. None of these contributed to the B/R summary ROC curve.<br><br>The quality assessments of the prospective studies were summarised; there was a lack of studies with comprehensive data for both groups, as reported above. Fewer than half of the DA and of the B/R studies adequately described the type of lesions shown to participants. A third of the DA studies showed at least one early-stage melanoma, while a third showed at least one late-stage melanoma. 11% of the DA studies had an appropriate study size, whereas none of the B/R studies did. | were included as dermatologists and as physicians.<br>Summary of results in text poorly reported as some numerical errors. Results taken from tables of studies rather than text.<br><br>Authors conclude that the currently available data are insufficient to support any policy regarding use of either a gatekeeper system or direct access to dermatologists.<br><br>Search strategy to include studies 1966 – 1999. Review included some studies > 20 years old (some in 1950s). | |
| (Cox 2004). | To determine the views of dermatologists, with audit and database information where possible, on the overall impact of the two-week rule referral standard for suspected skin cancers. | Audit, using a questionnaire, sent to consultant dermatologists in the U.K., requesting views and numerical data. | 272 U.K. dermatologists reporting on data on patients with malignant and benign skin lesions.<br><br>**UK** | Dermatologists' views on the two-week rule, and proportions of specific lesion types referred under the rule: especially melanoma and SCC, but also benign lesions. | There were 139 responses, some on a departmental basis, representing 272 individuals (nearly two thirds of all consultant dermatologists in post in the U.K). Based on 52 formal audit studies or database information, the overall proportion of confirmed skin cancers amongst two-week rule referrals was 12%, but only 42% of tumours were referred by this route. Correct suspicion of melanoma was generally better than that of SCC. Information on standard referral proformas was only considered to be 'usually adequate' by 34% of departments. Considering all replies, only 27% of respondents felt that the two-week rule works well; the major problems are an excess of benign lesions, the lack of opportunity to prioritise referrals and the displacement of other urgent problems. Author | 139 responses were received (rate 64%), 52 of which included audit data. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | concludes that there are significant problems with the perception and application of the two-week referral standard for possible skin cancers, including high volume of non-relevant lesions and displacement of other urgent conditions. Increasing the specificity of referral guidelines, and increased education regarding recognition of benign lesions, are the favoured options for improvement. | | |
| (Del Mar & Green 1995) | To test whether the provision to doctors of a diagnostic algorithm and Polaroid camera improved the differential diagnosis of melanoma by leading to a reduction of benign pigmented lesions excised, without affecting the excision rate of malignant lesions. | Randomised controlled 'field trial' i.e. ecological study undertaken over 2 years:<br><br>Intervention city: Doctors provided with diagnostic algorithm and Polaroid camera to monitor lesions over time.<br><br>Control city: Standard practice. | 114 Doctors performing skin surgery (predominantly GPs) in Queensland.<br><br>Randomised unit was the city (n=2).<br><br>**Australia** | Audit of all pathological reports undertaken for both cities to measure:<br><br>% of benign (i.e. classed as neither malignant nor potentially malignant) melanocytic lesions excised.<br><br>Analysis performed at baseline (pre intervention) and post intervention. | There was no significant difference in the % of benign lesions reported in the intervention and control cities before the algorithm and camera were used (93.6% and 94.0% respectively).<br><br>After the intervention the % of excised lesions that were neither malignant nor potentially malignant fell in both cities:<br><br>From 94% to 93.8% in the control city (difference of 0.2%)<br><br>From 93.6% to 88.8% in the intervention city (difference of 4.8%). The decrease was significantly different between cities ($p < 0.001$).<br><br>Significantly fewer doctors in the intervention city than the control city offered exclusion of malignancy as the reason for excision ($p < 0.0001$).<br><br>Authors conclude that clinical diagnostic accuracy for melanocytic lesions is enhanced through use of an algorithm and camera. | Analysis undertaken blind to intervention / control status. | 1 - |
| (Duff *et al.* 2001) | To investigate the effectiveness in making and excluding the diagnosis of melanoma in a PLC. | Observational study. | 9968 patients attending a PLC between 1993-1998.<br><br>**UK** | Diagnostic accuracy: sensitivity and specificity and negative predictive value. | 586 melanomas were diagnosed; 24.7% of excisions led to the diagnosis of melanoma. 7 invasive melanomas and 2 lentigo malignas were missed. There was one histological false negative.<br>The PLC has a sensitivity 98.5% and specificity of 89.2% for the diagnosis of melanoma; the negative predictive value is 99.9%. | Diagnoses made by one of two consultant plastic surgeons with a dermatoscope. | 3 |
| (English *et al.* 2003) | To determine whether an aid to the diagnosis of | RCT with randomisation by | Participants were GPs. | Ratio of benign pigmented lesions to | At baseline the ratios of benign to malignant lesions were lower in the | Reviewer's comment: Unclear whether reported results for | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | pigmented skin lesions reduces the ratio of benign lesions to melanomas excised in general practice. | practice. Intervention practices were given an algorithm and instant camera to assist with the diagnosis of pigmented skin lesions i.e. lesions identified as benign by the algorithm were photographed and reviewed as an alternative to excision. All practices were given national guidelines on managing melanoma. | **Australia** | melanomas excised with Odds Ratio. Analyses conducted with and without inclusion of seborrhoeic keratoses, which are commonly mistaken for melanoma. | intervention group than in the control group. During the trial period the ratios were higher in the intervention group (19:1 v 17:1 without seborrhoeic keratoses and 29:1 v 26:1 with seborrhoeic keratoses). After adjustment for patients' age, sex, and socioeconomic status, the ratio was 1.02 times higher (95% confidence interval 0.68 to 1.51, P = 0.94) in the intervention group when seborrhoeic keratoses were not included and 1.03 times higher (0.71 to 1.50, P = 0.88) when seborrhoeic keratoses were included. General practitioners in the intervention group were less likely than those in the control group to excise the most recent pigmented skin lesion they managed (22% v 48%, p < 0..001) and to refer the patient to a specialist (16% v 27%, P = 0.06). Authors concluded that provision of the algorithm and camera did not decrease the ratio of benign pigmented skin lesions to melanomas excised by general practitioners. | last lesion managed add useful information. 5 GPs worked at practices in both randomised groups. Groups differed in terms of socioeconomic status of patients cared for. GPs joined the trial after randomisation; more so into the intervention arm. Limited Generalisability to UK since this NICE guidance does not recommend that GPs excise lesions suspicious of melanoma. | |
| (Gerbert *et al.* 1998) | To determine whether a brief, multicomponent educational intervention could improve the skin cancer diagnosis and evaluation planning performance of primary care physicians to a level equivalent to that of dermatologists. | RCT<br><br>Intervention group (n=26): Provided wit educational seminar, diagnostic written material and equipment for clinical examination and feedback on performance.<br><br>Control group (n=26):<br><br>Plus 13 dermatologists. | 52 primary care physicians plus 15 dermatologists.<br><br>**US** | Primary care physicians' ability to diagnose and plan management of patients with skin cancer, pre-test and post-test.<br><br>6 categories of skin lesion were evaluated, including melanoma, SCC and BCC.<br><br>Participants were required to choose from six treatment options, which did not include 'refer to dermatologist'.<br><br>Evaluation was at pre-test, intervention and post-test periods. | All three groups demonstrated improved performance through the study period.<br><br>At post-test, both the intervention and control group demonstrated improved performance, with the intervention group revealing significantly larger gains.<br><br>The intervention group showed greater improvement than the control group across all six diagnostic categories of lesion (a gain of 13 percentage points vs. 5, p < .05),, and in evaluation planning for melanoma (a gain of 46 percentage points vs. 36, p < .05) and SCC (a gain of 42 percentage points vs. 21, p < .01).<br><br>The intervention group performed as well as the dermatologists on five of the six skin cancer diagnosis and evaluation planning scores with the exception of the diagnosis of BCC. | Sample and recruitment methods not described.<br><br>There were no significant differences between participants at the start of the study for demographic, dermatology experience and pre-test ability variables.<br><br>Dermatologists did not receive the intervention.<br><br>Some patients with lesions were examined, other lesions (especially melanoma) were examined on slides.<br><br>Of 62 initial participants recruited, 10 primary care physicians retired from the study before the post-test (5 from intervention and 5 from control groups). | 1 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | The authors concluded that primary care physicians can diagnose and make evaluation plans for cancerous skin lesions, including melanoma, at a level equivalent to that of dermatologists if they receive relevant, targeted education. | | |
| (Gerbert *et al.* 2002) | To test whether the educational intervention on skin cancer diagnosis and treatment planning designed by Gerbert et al. (1998) improved the diagnostic and management ability of primary care physicians when used via the internet. | RCT<br><br>Intervention (n=39): Pre-test, internet tutorial (including melanoma, SCC, BCC and non malignant lesions), post test I and further post test II 8 weeks later.<br><br>Control (n=32): Pre-test followed by post test I. | 71 primary care physicians.<br><br>**US** | % of correct answers in pre test and post test, analysed by lesion type for:<br><br>Diagnosis<br><br>Management decision.<br><br>Effect of intervention on sample as a whole (non ITT) in subjective confidence (data not shown). | From pre-test to post test I, the intervention group showed significantly greater improvement than control group in overall diagnosis and evaluation planning, diagnosis of melanoma and seborrhoeic keratosis, diagnosis and evaluation planning of SCC and BCC and evaluation planning for actinic keratosis.<br><br>In post test II (intervention group only) this advantage was maintained for diagnosis of melanoma, diagnosis and evaluation planning of SCC, overall evaluation planning and evaluation planning for BCC.<br><br>Authors conclude that the internet is an effective medium for training of primary care physicians in the diagnosis and management planning of skin lesions including melanoma, SCC and BCC. | Only univariate statistical tests used – possible type I errors in numerous (14) outcomes, although some results were significant at $p < 0.01$ or $p < 0.001$.<br><br>Of 879 initial study accruals only 71 completed the study in full.<br><br>The control group underwent the tutorial after the post test (which should not affect results).<br><br>A greater proportion of the intervention group worked primarily in medical schools.<br><br>In this study, primary care physicians in private practice were under represented. | 1 + |
| (Gerbert *et al.* 1996) | To measure the readiness of primary care physicians to triage 37 lesions suspicious for skin cancer.<br><br>To assess the difference in diagnostic ability between primary care physicians and dermatologists.<br><br>To assess diagnostic accuracy using three different methods of examination: slide, computer image and patient examination. | Cross sectional survey of diagnostic ability, comparing primary care physicians and dermatologists.<br><br>Lesions viewed included melanoma (on slide / computer image only), NMSC and benign lesions. 25 identical lesions were shown by each method, plus 12 additional melanoma lesions by non patient methods only. | 71 primary care physicians and 15 dermatologists (11 residents plus 4 attending physicians).<br><br>12 patients with NMSC or lesions requiring differential diagnosis for NMSC.<br><br>**US** | Summary scores of diagnostic and treatment planning ability:<br><br>Between primary care physicians and dermatologists.<br><br>For 6 different lesion categories (nevi, melanoma, SCC, BCC, seborrhoeic keratoses, actinic keratoses).<br><br>By each of 3 methods of viewing the lesion. | Dermatologists performed significantly better than primary care physicians in diagnosing all 6 categories of lesion and formulating treatment plans.<br><br>For primary care physicians, having worked in a dermatology clinic (OR 8.32, 95% CI 1.8-23.2) was associated with higher scores for diagnosis (defined as above the median).<br><br>Both primary care physicians and dermatologists improved in diagnostic / planning scores with repeated exposure to the lesions by the three methods.<br><br>Primary care physicians' diagnostic error rate was 50% for melanoma and NMSC, compared with 19% for | 71/84 (85%) GPs contacted, participated in the study.<br><br>11/11 resident dermatologists contacted, participated in the study.<br><br>4/6 attending dermatologists contacted, participated in the study.<br><br>Participants were randomised to 1 of 6 different sequences of methods, to control for 'order of method' effect.<br><br>For the 25 lesions viewed on patients, histological confirmation was obtained. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | dermatologists (statistical significance not reported). These values for treatment / biopsy planning were 33% and 19% respectively (statistical significance not reported).<br><br>Authors conclude that primary care physicians are inadequately prepared to diagnose and evaluate lesions suspicious of skin cancer. | Study lesions included diagnostically difficult lesions. | |
| (Jackson *et al.* 2000) | To audit all melanomas confirmed histologically in one health district over 6 years. | Observational study. | 157 melanomas.<br><br>**UK** | | *Excision:*<br>GPs: 37%; hospital specialists: 63%<br>*Clinical diagnosis of melanoma:*<br>GPs: 9%; hospital specialists: 35%<br>*Clinical diagnosis of suspicious PSL:*<br>GPs: 45.5%; hospital specialists: 38%. | | 3 |
| (Jemec 1999) | To investigate the diagnostic accuracy of GPs in diagnosing Pigmented skin lesions. | Prospective study. | 27 trained or trainee GPs.<br><br>Participants shown 20 slides for 20 seconds each and asked to assess malignant or non-malignant.<br><br>**Denmark** | Sensitivity, specificity and positive prognostic value. | The median diagnostic accuracy (sensitivity) for the group as a whole was 0.75 (95% CI 0.65-0.80), the specificity was 0.70 (95% CI 0.68-0.79) and the positive predictive value 0.70 (95% CI 0.62-0.77). | Selection bias - GP population comes from those attending a seminar on skin cancer. | 3 |
| (Julian 1999) | To determine the nature and frequency of skin disease seen in general practice. | Retrospective case series analysis of data collected over a 5 year period at a general practice in Cornwall. | Single GP with an interest in dermatology.<br><br>Case mix: 11,191 patients seen at a single practice over a 5 year period of which 2386 presented with skin disease.<br><br>**UK** | Proportion of patients with skin disease of various types, listed by specific condition, including NMSC. | 21% of all patients seen at the practice had skin disease, increasing from 16% in 1989 to 37% in 1994.<br><br>Of 2386 patients with skin disease, 74 had skin cancer (3%):<br><br>Melanoma: 2 (2.7% of skin cancers)<br>SCC 10 (13.5% of skin cancers)<br>BCC 62 (83.8% of skin cancers)<br><br>All malignant tumours were treated at the practice and all surgical specimens were sent for histological confirmation. | Useful to this research question only in terms of providing an estimate of the numbers of SCC, BCC and melanoma observed in a UK general practice with a GP with dermatological interest.<br><br>Does not measure the diagnostic performance of the GP compared with the histological finding. | 3 + |
| (Lindelof *et al.* 1998) | To assess how well dermatologists recognise malignant melanomas in patients with naevi. | Retrospective study. | 9,121 patients diagnosed with melanocytic naevi.<br><br>**Sweden** | Records of malignant melanoma (from the Cancer Registry). | 113 cases of melanoma were detected in the study population. 60 patients were diagnosed with melanoma prior to the naevus diagnosis and most of them were under continuous follow-up. A further 35 patients were diagnosed with melanoma and naevus at the same | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | time. The remaining 18 were given the diagnosis melanoma after the naevus diagnosis and, of these, 6 cases were detected more than 6 years after examination and melanoma was considered not present at the time of consultation. Three cases can be considered as missed (6%) and four others as partially missed or delayed. Of 47 cases of probable recognisable melanoma, there was insufficient management of 7 (15%). 6 cases were detected during dermatological examination for other conditions and 5 through general examination of naevi. | | |
| (Morrison *et al.* 2001) | To compare the diagnoses of GPs and dermatologists over a selected period in patients with a possible diagnosis of skin cancer referred to a skin cancer screening clinic. | Retrospective observational study. | 493 patients attending a skin cancer screening clinic in a 12 month period.<br><br>**Ireland** | Comparison of diagnoses of GPs and dermatologists. | All clinical diagnoses of GPs and dermatologists agreed in 54% of cases.<br>38/493 had histologically proven skin cancers:<br>20 BCCs:<br>GPs correct in 40%, dermatologists correct in 95% cases<br>9 SCCs:<br>GPs correct in 22%, dermatologists correct in 77% cases<br>8 melanomas:<br>GPs correct in 25%, dermatologists correct in 75% cases. | Small numbers of malignancies. | 3 |
| (Morton & MacKie 1998) | To determine diagnostic accuracy in a dedicated PLC; to assess impact on accuracy of dermatology experience and tumour thickness. | Retrospective observational study. | 1999 biopsies performed at a PSL clinic during a 2 year period.<br><br>**UK** | Diagnostic accuracy, index of suspicion, sensitivity, specificity and positive predictive value. | Diagnostic accuracy for 2 dermatologists with > 10 years experience was 80% (sensitivity 91%, positive predictive value 86%)<br>Diagnostic accuracy for 2 specialist registrars with 3-5 years experience was 62%.<br>Diagnostic accuracy for 6 registrars with 1-2 years experience was 56%<br>Thin and intermediate thickness melanomas generated greatest inaccuracy irrespective of experience. | | 3 |
| (Offidani *et al.* 2002) | To assess the ability of general practitioners (GPs) in the early diagnosis of skin cancers, their correct differential diagnosis of benign lesions and their accuracy in the choice of the treatment. | Cross sectional survey of diagnostic ability of GPs for skin cancer.<br><br>GPS received four images of skin lesions plus seven | 288 responding GPs out of 625 GPs who were sent the questionnaire.<br><br>**Italy** | GPs' diagnostic ability for melanoma, SCC, BCC and seborrhoeic keratoses.<br><br>GPs' ability to state correct therapeutic | A mean of 115 patients per GP made consultations for dermatological conditions per year.<br><br>1% of GPS reported 'good' confidence in their diagnostic ability. 31% reported 'slight' confidence and confidence was significantly higher according to a greater number of dermatological | The sample of GPs had been practicing for approximately 17 years on average. Younger GPs appeared less likely to respond compared to middle aged GPs whereas the oldest GPs were reported as 'scarcely interested'. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | clinical case descriptions and a multiple choice questionnaire. | | action for above lesions.<br><br>Self reported opinion on ability to diagnose skin cancers. | cases seen per year.<br><br>103 (36%) GPs correctly diagnosed seborrhoeic keratoses.<br>118 (41%) GPs accurately recognised BCC and proposed correct intervention.<br>153 (53%) GPs correctly diagnosed SCC.<br>262 (91%) of GPs correctly identified melanoma.<br><br>Authors conclude: Many GPs are not confident in their ability to recognise the most common skin cancers, and knowledge deficiencies were identified. | The small number of images viewed permits a simple assessment of diagnostic ability of 'classic' and fairly distinct lesions.<br><br>Response rate is low: 288/625 (46%). | |
| (Osborne *et al.* 2003) | To compare the false-negative rate of clinical diagnosis in a PLC with that of other clinics of primary referral for melanoma. | Retrospective observational study. | 731 melanomas over a 10 year period.<br><br>**UK** | False-negative rate of diagnosis: false-negative clinical diagnoses/ true-positive histological diagnoses. | False negative rates:<br>PLC 10%<br>Dermatology clinics 29%<br>Plastic surgery clinics 19%<br>Other clinics 55%<br>GPs 54%<br>($p < 0.0001$)<br><br>Frequencies of risk factors for diagnostic failure:<br>PLC 20%<br>Dermatology clinics 25%<br>Plastic surgery clinics 22%<br>Other clinics 31%<br>GPs 30%<br><br>False negative rates for lesions exhibiting each risk factor, PLC had the lowest rate in every case (PLC vs. all clinics combined, $p = 0.04$ to $p < 0.0001$)<br>Mean FNR for combined risk factors:<br>PLC 18%<br>Dermatology clinics 45%<br>Plastic surgery clinics 50%<br>Other clinics 68%<br>GPs 71%<br><br>In the 500 patients in the PLC, melanoma pick-up rate on biopsy was 32% and diagnostic FPR was 41%. | | 3 |
| (Raasch *et al.* 2000) | To test whether auditing and providing feedback (on diagnostic and management ability) to | RCT undertaken over 9 months.<br><br>Doctors underwent | 46 primary care physicians, audited on the treatment of 1366 patients and | Mean no. of correct clinical diagnoses.<br><br>Mean certainty of | There was no significant change within or between groups for mean proportion of correct clinical diagnoses per doctor. | Of 91 eligible doctors, 46 were randomised.<br><br>Doctor groups similar at | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | primary care physicians improves their performance. | Pre and post testing either side of feedback intervention.<br><br>Intervention (n=23) doctors provided with audit feedback on their performance.<br><br>Control (n=23) doctors audited but not provided with feedback until after the study had concluded. | 1416 skin lesions.<br><br>Physicians had to work 3 or more sessions per week in primary care to be eligible.<br><br>**Australia** | diagnosis score.<br><br>Mean no. of inadequate excisions per doctor.<br><br>Mean no. of pathology results with no clinical diagnosis recorded.<br><br>PPV and Sensitivity with regard to malignant and benign lesions. | Both intervention and control groups significantly improved for certainty of diagnosis score and mean no. of inadequate excisions, but with no significant difference between groups.<br><br>The intervention group showed a significantly greater improvement than the control group for the mean no. of pathology requests submitted without clinical diagnoses.<br><br>There were no significant differences between groups for PPV of diagnoses.<br><br>The only significant difference for sensitivity of diagnosis was for benign lesions only, at pre-test stage only, between intervention and control groups.<br><br>Authors conclude that patient factors confounded the study such that very little difference was observed between randomised groups. | outset but for number of doctors per practice (more in control).<br><br>Patients treated in each group differed: more young patients, female patients and those with histologically or clinically malignant diagnoses were seen in the intervention group.<br><br>3 doctors in the control group dropped out or provided no data. This figure for the intervention group was 2.<br><br>Power calculation based upon 356 patient consultations.<br><br>Doctors consented to trial participation but were not told their randomised arm. Doctors knew of audit since they obtained patient consent for review of records by the researcher.<br><br>Possible Hawthorne effect since all doctors knew of audit. Similarly if randomised individually (not clearly reported) doctors within the same practice could discuss the trial. | |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | **Recommends:**<br><br>Patients with lesions suspicious of melanoma should be referred urgently to a dermatologist or surgeon / plastic surgeon with an interest in pigmented lesions.<br><br>These specialists should ensure that a system is in place to enable patients with suspicious lesions to be seen within 2 weeks of receipt of the referral letter. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Scottish Intercollegiate Guidelines Network | To provide advice to health professionals | Evidence based guidelines, with | Patients with melanoma. | Recommendations for practice. | **Recommends:** | Guideline development was based upon a | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| 2003) | involved at all stages of care of patients with melanoma. | recommendations graded according to the quality of evidence available. | **UK** | | Clinicians should be familiar with the seven point checklist used to assist diagnosis of melanoma. | multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | |

**The question**

*In patients with pigmented skin lesions, do General Practitioners (GP), General Practitioners with a Special Interest in Dermatology (GPSI) or Dermatologists perform the most adequate removal / excisions?*

**The nature of the evidence**

Eight studies were identified, as follows:

- Seven observational studies (four of fair quality and three of good quality)
- One clinical guideline of good quality

Six studies originate from the UK and one study each is from the US and New Zealand. Applicability to the UK is therefore good.

Three studies are of patients who underwent minor surgery to treat melanoma. One study was of patients treated in general medicine or dermatology departments for skin conditions (including skin cancer) and one study was of patients who underwent skin biopsy.

**Summary of the supporting evidence for the recommendations**

**There is observational study evidence that patients prefer to be treated by dermatologists for dermatological conditions than by GPs. Observational study evidence is suggestive that GPs are more likely to perform incomplete excisions of melanoma tumours than hospital based specialists, and that GPs do not routinely obtain histological examination of skin lesions which they believe to be benign. Evidence from a retrospective, observational study suggests a survival advantage for patients in whom melanoma is surgically treated by dermatologists compared to general and plastic surgeons. This study did not demonstrate a significant difference in outcome between patients treated by GPs compared to the other groups. Evidence from one observational study in New Zealand suggests that cases of melanoma are infrequently seen in primary care and that not all melanoma tumours are adequately excised in primary care. Audit evidence supports the recommendation that GPs refer patients with lesions suspicious of melanoma to a specialist for treatment. Clinical guidelines for the treatment of patients with melanoma produced by the British Association of Dermatologists are strongly supportive of specialists carrying out excision of melanoma and recommend**

**immediate specialist referral of patients who have pigmented lesions excised in primary care which are subsequently reported as melanoma.**

- The cross-sectional survey of patients' views by Federman et al. (2001) found that dermatology patients were more confident in the ability of dermatologists in performing procedures (treat rashes, diagnose skin cancer, perform skin biopsies, use liquid nitrogen, perform surgery) compared with primary care practitioners.

- The retrospective case series study by Herd et al. (1992) found that patients with melanoma tumours excised by GPs were younger and had tumours with smaller diameters than patients treated in hospital. Breslow thicknesses were similar between groups. Completeness of initial excision was more frequently doubtful or incomplete in GP excisions compared with hospital excisions. Melanoma was a suspected diagnosis in 15% of GP cases and 79% of hospital cases.

- The retrospective case series study by Khorshid, Pinney, and Bishop (1998) found that incomplete excision was significantly more likely following GP excision than hospital excision. GPs made a confident clinical diagnosis of melanoma in 17% of patients prior to surgery. Half of the GPs reported that they felt confident enough to manage patients with suspected skin cancers on their own and the majority of GPs did not routinely obtain histological examination of skin lesions they believed to be benign.

- The retrospective study by McWilliam et al. (1991) found histological malignancy to be more common in tumours excised in hospital than by GPs. Completeness of excision was significantly less common among tumours excised by GPs than those excised by hospital surgeons.

- The large, retrospective study by McKenna et al. (2004) compared survival, according to 4 types of treating physician and found that overall survival, disease free survival and recurrence free interval were significantly different across all the groups, using, with all three measures best in the dermatology group. The study did not demonstrate a statistically significant survival disadvantage for patients treated by GPs relative to dermatologists.

- The audit by the Specialist Clinical Audit Programme for South London, Kent, Surrey and Sussex (2002) recommended that GPs should refer all suspicious

melanocytic lesions to a dermatologist or surgeon with a specific interest in melanocytic lesions with full clinical details completed on the request form. They also recommended that melanoma specialists should be readily available to GPs for referral purposes.

- Clinical guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists recommend that all patients who have had lesions removed by their general practitioner that are subsequently reported as melanoma should be referred immediately to specialists.

- The prospective case series study by Corwin, Munn, and Nicholls (1997) studied 28 GPs in New Zealand over a 5 month period and found that three melanoma tumours were observed and treated in primary care, of which one was incompletely excised (incomplete excision rate 33.3%).

# EVIDENCE TABLE 3.2

***In patients with pigmented skin lesions, do General Practitioners (GP), General Practitioners with a Special Interest in Dermatology (GPSI) or dermatologists perform the most adequate removal / excisions?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| (Corwin *et al.* 1997) | To evaluate skin surgery undertaken by GPs by review of histology samples sent to a single pathology department. | Prospective case series of samples received from a random sample of GPs who performed surgery, studied over a 5 month period. | 28 participating GPs.<br><br>**New Zealand** | Completeness of excision.<br><br>Clinical diagnostic performance. | Audit forms were completed by participating GPs for 214 (70%) of 303 specimens submitted.<br><br>Of the 303 lesions, histological diagnosis was:<br>BCC 29<br>SCC 28<br>Melanoma 3<br>Cutaneous lymphoma 1<br><br>Malignant: benign ratio in the 303 lesions submitted was 61/242 i.e. approximately 1:4.<br><br>Incomplete excision rates were:<br>BCC 8/29 (27.6%)<br>SCC 10/28 (35.7%)<br>NMSC 18/57 (31.6%)<br>Melanoma 1/3 (33.3%)<br><br>Authors conclude that GPs in New Zealand undertake more skin surgery and to a higher standard than their counterparts in the UK, yet there is room for improvement. | In addition to the 303 specimens received, 28 patients were identified as referred to specialists for treatment (likely to be an under estimate).<br><br>Sensitivity and specificity calculated from Table 1 in paper.<br><br>Lesions that underwent diagnostic biopsy were not counted as incompletely excised.<br><br>Of 29 GPs randomly sampled, 1 declined to participate.<br><br>Histology used as gold standard. | 3 ++ |
| (Federman *et al.* 2001) | To ascertain the patient's perspective on dermatologic care provided by primary care providers (PCPs) or dermatologists. | Cross-sectional survey. | 133 general medicine clinic patients and 100 dermatology clinic patients.<br><br>**US** | Patient confidence. | Patients more confident in dermatologists' abilities to perform procedures (treat rashes, diagnose skin cancer, perform skin biopsies, use liquid nitrogen, perform surgery) compared with PCPs ($p < 0.001$). | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| (Herd *et al.* 1992) | To examine management of patients who had a melanoma excised initially by GPs in SE Scotland over 10 years and to assess impact of the 1990 contract on this. | Retrospective case series (population-based study). | All patients in SE Scotland who had melanoma tumours excised in 1982-91.<br><br>**UK** | Demographic details; Breslow thickness, clearance of excision. | 42 patients had Melanoma tumours excised by GPs in 1982-91. These patients were significantly younger than those who had their tumours excised initially in hospital. Largest diameter of Melanoma tumours excised by GPs was significantly less than of those excised in hospital, Breslow thicknesses were similar. Completeness of initial excision was doubtful or incomplete in 9 (23%) GP excisions cf. 4% of hospital excisions, but the time interval between excision biopsy and wide excision was similar. melanoma suspected in 15% (6/40) of GP cases cf. 79% of hospital cases. | Authors conclude that GPs need to think more often of melanoma when they excise pigmented lesions and when they consider this tumour a possibility should perform an excision biopsy with a lateral clearance of at least 2 mm. | 3 |
| (Khorshid *et al.* 1998). | To identify all cases of cutaneous melanoma excised by GPs between 1989-1994 and review patient management. | Retrospective population-based case series. | 819 Melanoma tumours excised in NE Thames region by GPs.<br><br>**UK** | Patterns of distribution of GP excisions within the region.<br><br>Histological subtypes of Melanoma tumours excised, accuracy of the pre-excision clinical diagnosis and adequacy of treatment of GP-treated tumours cf. control group.<br><br>Reported current practice in the management of pigmented skin lesions by the GPs who had excised Melanoma tumours. | 819 Melanoma tumours were excised, of which 59 were excised by GPs. Breslow thickness of tumours was similar in both GP-excised and non-GP-excised groups. Tumours were more likely to be amelanotic in the GP-excised group ($p < 0..001$). Incomplete excision was significantly more likely in the GP group ($p < 0..001$). GPs made a confident clinical diagnosis of melanoma in 17% of patients prior to surgery. Reported referral rate to specialists by this subset of GPs of patients with pigmented lesions was low, and at interview half of the GPs reported that they felt confident enough to manage patients with suspected skin cancers on their own. Majority of GPs did not routinely obtain histological examination of skin lesions they believed to be benign. | Problems with the accuracy of clinical diagnosis and inadequacy of excision of melanomas removed in primary care. | 3 |
| (McWilliam *et al.* 1991) | To evaluate and appraise skin biopsies performed by GPs and compare their performance with that of hospital doctors. | Retrospective analysis of histology records between 1989 and 1991.<br><br>Examination of computer records for the years 1984–1989. | Records of 292 skin biopsy specimens obtained by GPs and 324 specimens obtained by hospital doctors.<br><br>Results represent specimens of all skin biopsy samples, including skin cancer and benign | Clinical and pathological diagnoses and completeness of excision.<br><br>Quality of information provided on request cards, by assigning a score of poor, average or | The number of specimens received from surgeons and GPs increased over the study period of 1984-1990; the proportion of specimens from GPs rose from 17/1268 (1.3%) in 1984 to 201/2387 (8.7%) in 1990.<br><br>The range of diagnoses was similar among hospital and general practitioner cases, although malignancy was commoner in hospital cases (63/324 (19%) v 14/292 (5%) in general | Total numbers are used rather than samples, although hospital cases of specimens from lesions >3.0 cm in diameter excluded, to optimise comparability with samples from primary care.<br><br>Very little information provided by lesion type. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | skin lesions.<br><br>**UK** | good. | practitioner cases; chi 2 = 28, p < 0.00001).<br><br>The quality of clinical information given on request forms was similar between groups.<br><br>Accuracy of clinical recognition of lesions was significantly less among GPs compared to hospital doctors (p < 0.00001).<br><br>In 41% of cases there was good agreement between GPs clinical diagnosis and histopathological findings; the figure for hospital cases was 62%.<br><br>Completeness of excision was less common among general practitioners than hospital surgeons (150/233 (3/15 malignant) v 195/232 (57/63) p < 0.00001).<br><br>Authors conclude that the performance of skin biopsy by GPs could be improved and that all skin specimens should be sent for histological examination. | | |
| (McKenna *et al.* 2004) | To compare clinicopathological characteristics of patients with melanoma and survival, according to 4 types of specialist providing treatment. | Retrospective, observational case series study over a 19 year period, interrogating a database. | 1536 patients with primary, invasive, cutaneous melanoma with no evidence of metastasis at time of surgery.<br><br>**UK** | Treatment proportions were dermatologist 43%, general surgeon 32%, plastic surgeon 17% and GP 8%. Outcome measures were overall survival (OS), disease free survival (DFS) and recurrence free interval (RF). | Over 90% of patients managed by a dermatologist or GP underwent wider local excision following initial excision, compared to 43% in the general surgery group and 25% in the plastic surgery group. General surgeons made the widest excision margins in single stage and in two stage excision. Overall survival at 5 and 10 years was better in the dermatology and GP groups than the surgical groups (p < 0.0001), by log rank test. Overall survival, disease free survival and recurrence free interval were significantly different across all the groups, using dermatologists as the reference group, with all three measures best in the dermatology group (p < 0.0001) in the Cox Proportional Hazards Model, controlling for measurable prognostic factors. There was however no significant difference in these outcomes comparing | Appraised with 'Qualitative' checklist designed by NICE. No estimate of precision/p value for excision margins provided. Small numbers in GP group [8% =123].<br><br>General surgeons and plastic surgeons treated poorer prognosis patients.<br><br>Patients who underwent a second stage excision (found elsewhere to carry a survival advantage) were over represented in the dermatology group.<br><br>Study does not conclude whether patients managed by GPs have a poorer outcome. | 3+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | GPs and any single other group. Authors recommend that dermatologists should have a central role in melanoma management. | Effect of GPs with interest in dermatology is not known.<br><br>GPs likely to have treated lesions at an earlier stage than other groups: possible lead time bias. | |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | **Recommends:**<br><br>All patients who have had lesions removed by their general practitioner that are subsequently reported as melanoma should be referred immediately to specialists. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Specialist Clinical Audit Programme for South London 2002) | • To audit standard of histopathology reporting against South Thames Health Authorities melanoma report (see 1996–1998, and 2000) and UK Melanoma Study Group guidelines<br>• To identify source of referral for histopathology melanoma reporting<br>• To identify histology reporting procedures used across the region<br>• To meet the requirements of the referring clinician to determine prognosis and further patient treatment<br>• To achieve the minimum recommended requirements of histopathology reporting for cutaneous melanoma<br>• To recommend factors that may improve the process used in the reporting of melanoma by histopathology | Audit of histopathology departments in South London, Kent, Surrey and Sussex. | Phase 1:<br>Patients with skin cancer treated within acute Trusts.<br><br>**UK** | Outcomes audited included tumour characteristics, completeness of excisions, surgical procedures performed. | Recommendations:<br>• GPs should refer all suspicious melanocytic lesions to a dermatologist or surgeon with a specific interest in melanocytic lesions<br>• Pigmented lesion clinics staffed by melanoma specialists should be readily available for GPs to refer patients<br>• Curettage, punch biopsies, shave and incisional biopsies should not be performed on melanocytic lesions<br>• Request forms should contain full clinical details (minimum dataset requirements)<br>• Only 61% of responses stated that multidisciplinary meetings were held to discuss all melanoma cases. This practice should be adopted by all trusts<br>• Melanomas and difficult melanocytic lesions should ideally be reported by at least 2 pathologists<br>• Ideally, all melanomas should be reported by a specialist dermatopathologist<br>• Where this is not possible, reporting should be done by those seeing more than 1-2 Melanomas per year<br>• Suggestion that inexperienced departments should be part of a cancer network where a designated lab or labs report all melanomas for | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | departments. | | | | the network. | | |

## Non melanoma skin cancer

### The question

*What is the ability of General Practitioners to diagnose non melanoma skin cancer (NMSC)?*

### The nature of the evidence

Eighteen studies were identified, as follows:

- One systematic review of poor quality
- Three RCTs
- Thirteen observational studies, six of good quality, three of fair quality and four of poor quality.
- One expert opinion article

Six studies are from the UK and five are from the US. Three studies are from Australia, and the remaining studies are from Western Europe. Given the differences in primary care arrangements between the UK and other countries, applicability to the UK is limited. All studies pertain to patients with NMSC, although study participants are commonly clinicians. Some studies report on skin lesions, which include NMSC along with melanoma and benign skin lesions.

### Summary of the supporting evidence for the recommendations

**Two RCTs found that education of GPs is effective in increasing their diagnostic performance for NMSC. One trial showed that this education can be effectively deployed via the internet.**

**One RCT found little improvement in the diagnostic ability of GPs for skin lesions including NMSC arising from provision of feedback on their performance. However the intervention was associated with an improvement in terms of including clinical diagnosis with pathology request forms.**

**There is evidence from one systematic review undertaken of primary studies in the US that dermatologists are better able to diagnose NMSC than non dermatologists.**

**Four observational studies found that dermatologists are better able to diagnose NMSC than general practitioners. Audit evidence from the UK suggests that the two week referral rule for lesions suspicious of skin cancer has resulted in an excess of benign lesions referred to dermatology departments.**

- The RCT undertaken by Raasch, Hays, and Buettner (2000) found very little effect arising from an intervention whereby GPs in Australia were given feedback on their ability to correctly diagnose and manage malignant and benign skin lesions, since patient factors appeared to heavily confound the study. However the intervention was associated with a significant improvement in terms of including clinical diagnosis with pathology request forms.

- The RCT by Gerbert et al. (2002) found that an internet delivered educational intervention on skin cancer diagnosis and planning was associated with a significant improvement in the ability of GPs in overall diagnosis and evaluation planning, diagnosis of melanoma and seborrhoeic keratosis, diagnosis and evaluation planning of SCC and BCC and evaluation planning for actinic keratosis.

- The prospective case series study by Corwin, Munn E, and Nicholls (1997) found that 28 participating GPs in New Zealand correctly diagnosed 11/14 (79%) of BCC tumours and 9/19 (47%) of SCC tumours. Sensitivity for all lesions excised based upon malignant / benign diagnosis was 90.0% and specificity was 63.1%.

- The survey of UK dermatologists undertaken by Cox (2004) found that the two week referral rule for lesions suspected by GPs to be skin cancer has been associated with an excess of benign lesions referred to dermatology departments, resulting in a displacement of other urgent problems.

- The systematic review of 14 studies by Federman, Concato, and Kirsner (1999) found that dermatologists performed better than non-dermatologists in the diagnosis of images of benign and malignant skin lesions, with the proportion of correct diagnoses reported as 93% and 52% respectively, for the two groups of doctors.

- The RCT by Gerbert et al. (1998) found that an intervention group of primary care physicians showed greater improvement than the control group in the diagnosis of six diagnostic categories of malignant and non malignant skin lesions, including melanoma, SCC and BCC. The intervention group performed as well as a third

group of dermatologists on five of six diagnosis and treatment planning scores with the exception of the diagnosis of BCC.

- The cross sectional survey by Gerbert et al. (1996) concluded that dermatologists performed significantly better than primary care physicians in diagnosis of, and treatment planning for, SCC and BCC.

- The retrospective case series study by Julian (1999) reported that a single UK GP with an interest in dermatology saw, over a five year period, 10 cases of SCC and 62 cases of BCC.

- The prospective case series study by Lathlean (1999) demonstrated that a single GP in Australia had sensitivity of 77% for clinical diagnosis of NMSC, with an associated false negative rate of 5.8%.

- The retrospective study by McWilliam et al. (1991) found that accuracy of clinical recognition of lesions was significantly less among GPs compared to hospital doctors. In 41% of cases there was good agreement between GPs clinical diagnosis and histopathological findings; the figure for hospital cases was 62%.

- The case series study by Morrison, O'Loughlin, and Powell (2001) found that correct diagnosis of SCC was made by dermatologists in 75% of cases compared with 25% for GPs. These values for BCC were 95% and 40% respectively.

- The cross sectional survey by Offidani et al. (2002) found that 41% of GPs correctly diagnosed BCC and 53% of GPs correctly diagnosed SCC and concluded that many GPs are not confident in their ability to recognise the most common skin cancers.

- The prospective case series study by Raasch (1999) found that the clinical diagnosis of GPs was correct in 73.5% of BCCs (95% CI 64-83%) and 62.2% of SCCs (95% CI 57-68%).

- The retrospective analysis by Rodriguez et al. (2000) found that for BCC sensitivity of dermatologists was 91.4% and sensitivity of GPs was 41.4%. The specificity values were, respectively 96.4% and 70.9%.

- The retrospective audit by Schofield, O'Neill, and Tatnall (1993) found that GPs accurately diagnosed the skin cancer type in 2/14 cases (i.e. with sensitivity 14.3% compared with histology standard).

- The cross sectional study by Whited et al. (1997) found that using lesions as the unit of analysis the sensitivity of primary care physicians for malignant and non-malignant lesions was 38% (95% CI, 29%-47%), the specificity was 95% (95% CI, 93%-96%), the positive likelihood ratio was 7.1 (95% CI, 4.8-10.3), and the negative likelihood ratio was 0.66 (95% CI, 0.56-0.75).

# EVIDENCE TABLE 3.3

## *What is the ability of General Practitioners to diagnose NMSC?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Corwin *et al.* 1997) | To evaluate skin surgery undertaken by GPs by review of histology samples sent to a single pathology department. | Prospective case series of samples received from a random sample of GPs who performed surgery, studied over a 5 month period. | 28 participating GPs.<br><br>**New Zealand** | Completeness of excision.<br><br>Clinical diagnostic performance. | Audit forms were completed by participating GPs for 214 (70%) of 303 specimens submitted.<br><br>Of the 214 audit forms, 168 had a clinical diagnosis:<br><br>GPs correctly diagnosed 11/14 (79%) of BCC tumours and 9/19 (47%) of SCC tumours and 1/2 of melanoma tumours (50%).<br><br>Of the 303 lesions, histological diagnosis was:<br>BCC 29<br>SCC 28<br>Melanoma 3<br>Cutaneous lymphoma 1<br><br>For the 168 lesions submitted with a clinical diagnosis, sensitivity based upon malignant / benign diagnosis was 40/46 = 90.0%. Specificity was 77/122 = 63.1%.<br><br>Malignant: benign ratio in the 303 lesions submitted was 61/242 i.e. approximately 1:4.<br><br>Authors conclude that GPs in New Zealand undertake more skin surgery and to a higher standard than their counterparts in the UK, yet there is room for improvement. | In addition to the 303 specimens received, 28 patients were identified as referred to specialists for treatment (likely to be an under estimate).<br><br>Sensitivity and specificity calculated from Table 1 in paper.<br><br>Lesions that underwent diagnostic biopsy were not counted as incompletely excised.<br><br>Of 29 GPs randomly sampled, 1 declined to participate.<br><br>Histology used as gold standard. | 3 ++ |
| (Cox 2004) | To determine the views | Audit, using a | 272 U.K. | Dermatologists' | There were 139 responses, some on a | 139 responses were received | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | of dermatologists, with audit and database information where possible, on the overall impact of the two-week rule referral standard for suspected skin cancers. | questionnaire, sent to consultant dermatologists in the U.K., requesting views and numerical data. | dermatologists reporting on data on patients with malignant and benign skin lesions.<br><br>**UK** | views on the two-week rule, and proportions of specific lesion types referred under the rule: especially melanoma and SCC, but also benign lesions. | departmental basis, representing 272 individuals (nearly two thirds of all consultant dermatologists in post in the U.K). Based on 52 formal audit studies or database information, the overall proportion of confirmed skin cancers amongst two-week rule referrals was 12%, but only 42% of tumours were referred by this route. Correct suspicion of melanoma was generally better than that of SCC. Information on standard referral proformas was only considered to be 'usually adequate' by 34% of departments. Considering all replies, only 27% of respondents felt that the two-week rule works well; the major problems are an excess of benign lesions, the lack of opportunity to prioritise referrals and the displacement of other urgent problems. Author concludes that there are significant problems with the perception and application of the two-week referral standard for possible skin cancers, including high volume of non-relevant lesions and displacement of other urgent conditions. Increasing the specificity of referral guidelines, and increased education regarding recognition of benign lesions, are the favoured options for improvement. | (rate 64%), 52 of which included audit data. | |
| (Federman *et al.* 1999) | To measure and compare diagnostic performance of primary care physicians and dermatologists when faced with colour slides or high-quality transparencies of benign and malignant skin conditions. | Systematic review. | 14 primary studies of doctors diagnosing skin lesions in the US, representing 1823 doctors in total.<br><br>**US** | Provides combined estimates of proportion of diagnoses that were correct for each physician group. | Overall, dermatologists (93% correct) performed better than nondermatologists (52% correct) in the diagnosis of images of benign and malignant skin lesions ($P < .001$).<br><br>No significant difference was detected between dermatology residents (91% correct) and practicing dermatologists (96% correct) or between internal medicine residents (45% correct) and family practice residents (48% correct).<br><br>In addition, family medicine attending physicians (70% correct) performed better than internal medicine attending physicians (52% correct) ($P < .001$).<br><br>Authors conclude that primary care physicians should receive more training | Only studies of populations in the US were included therefore limited applicability to the UK.<br><br>Non randomised studies included.<br><br>The primary studies were likely to have included images of benign and malignant skin lesions and are not reported as SCC, BCC and melanoma.<br><br>Reference standard for measures of diagnostic performance is not included in study inclusion criteria. | 2 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | in the diagnosis of skin disease. | | |
| (Gerbert *et al.* 2002) | To test whether the educational intervention on skin cancer diagnosis and planning designed by Gerbert et al. (1998) improved the diagnostic and management ability of primary care physicians when used via the internet. | RCT<br><br>Intervention (n=39): Pre-test, internet tutorial (including melanoma, SCC, BCC and non malignant lesions), post test I and further post test II 8 weeks later.<br><br>Control (n=32): Pre-test followed by post test I. | 71 primary care physicians.<br><br>**US** | % of correct answers in pre test and post test, analysed by lesion type for:<br><br>Diagnosis;<br><br>Management decision;<br><br>Effect of intervention on sample as a whole (non ITT) in subjective confidence (data not shown). | From pre-test to post test I, the intervention group showed significantly greater improvement than control group in overall diagnosis and evaluation planning, diagnosis of melanoma and seborrhoeic keratosis, diagnosis and evaluation planning of SCC and BCC and evaluation planning for actinic keratosis.<br><br>In post test II (intervention group only) this advantage was maintained for diagnosis of melanoma, diagnosis and evaluation planning of SCC, overall evaluation planning and evaluation planning for BCC.<br><br>Authors conclude that the internet is an effective medium for training of primary care physicians in the diagnosis and management planning of skin lesions including melanoma, SCC and BCC. | Only univariate statistical tests used – possible type I errors in numerous (14) outcomes, although some results were significant at $p < 0.01$ or $p < 0.001$.<br><br>Of 879 initial study accruals only 71 completed the study in full.<br><br>The control group underwent the tutorial after the post test (which should not affect results)<br><br>A greater proportion of the intervention group worked primarily in medical schools.<br><br>In this study, primary care physicians in private practice were under represented. | 1 + |
| (Gerbert *et al.* 1998) | To determine whether a brief, multicomponent educational intervention could improve the skin cancer diagnosis and evaluation planning performance of primary care physicians to a level equivalent to that of dermatologists. | RCT<br><br>Intervention group (n=26): Provided with educational seminar, diagnostic written material and equipment for clinical examination and feedback on performance.<br><br>Control group (n=26):<br><br>Plus 13 dermatologists. | 52 primary care physicians plus 15 dermatologists.<br><br>**US** | Primary care physicians' ability to diagnose and plan management of patients with skin cancer, pre-test and post-test.<br><br>6 categories of skin lesion were evaluated, including melanoma, SCC and BCC.<br><br>Participants were required to choose from six treatment options, which did not include 'refer to dermatologist'.<br><br>Evaluation was at pre-test, intervention and post-test periods. | All three groups demonstrated improved performance through the study period.<br><br>At post-test, both the intervention and control group demonstrated improved performance, with the intervention group revealing significantly larger gains.<br><br>The intervention group showed greater improvement than the control group across all six diagnostic categories of lesion (a gain of 13 percentage points vs. 5, $p < .05$), and in evaluation planning for melanoma (a gain of 46 percentage points vs. 36, $p < .05$) and SCC (a gain of 42 percentage points vs. 21, $p < .01$).<br><br>The intervention group performed as well as the dermatologists on five of the six skin cancer diagnosis and evaluation planning scores with the exception of the diagnosis of BCC.<br><br>The authors concluded that primary care physicians can diagnose and make | Sample and recruitment methods not described.<br><br>There were no significant differences between participants at the start of the study for demographic, dermatology experience and pre-test ability variables.<br><br>Dermatologists did not receive the intervention.<br><br>Some patients with lesions were examined, other lesions (especially melanoma) were examined on slides.<br><br>Of 62 initial participants recruited, 10 primary care physicians retired from the study before the post-test (5 from intervention and 5 from control groups). | 1 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | evaluation plans for cancerous skin lesions, including melanoma, at a level equivalent to that of dermatologists if they receive relevant, targeted education. | | |
| (Gerbert *et al.* 1996) | To measure the readiness of primary care physicians to triage 37 lesions suspicious for skin cancer.<br><br>To assess the difference in diagnostic ability between primary care physicians and dermatologists.<br><br>To assess diagnostic accuracy using three different methods of examination: slide, computer image and patient examination. | Cross sectional survey of diagnostic ability, comparing primary care physicians and dermatologists.<br><br>Lesions viewed included melanoma (on slide / computer image only), NMSC and benign lesions. 25 identical lesions were shown by each method, plus 12 additional melanoma lesions by non patient methods only. | 71 primary care physicians and 15 dermatologists (11 residents plus 4 attending physicians).<br><br>12 patients with NMSC or lesions requiring differential diagnosis for NMSC.<br><br>**US** | Summary scores of diagnostic and treatment planning ability:<br><br>Between primary care physicians and dermatologists.<br><br>For 6 different lesion categories (nevi, melanoma, SCC, BCC, seborrhoeic keratoses, actinic keratoses).<br><br>By each of 3 methods of viewing the lesion. | Dermatologists performed significantly better than primary care physicians in diagnosing all 6 categories of lesion and formulating treatment plans.<br><br>For primary care physicians, having worked in a dermatology clinic (OR 8.32, 95% CI 1.8-23.2) was associated with higher scores for diagnosis (defined as above the median).<br><br>Both primary care physicians and dermatologists improved in diagnostic / planning scores with repeated exposure to the lesions by the three methods.<br><br>Primary care physicians' diagnostic error rate was 50% for melanoma and NMSC, compared with 19% for dermatologists (statistical significance not reported). These values for treatment / biopsy planning were 33% and 19% respectively (statistical significance not reported).<br><br>Authors conclude that primary care physicians are inadequately prepared to diagnose and evaluate lesions suspicious of skin cancer. | 71/84 (85%) GPs contacted, participated in the study.<br><br>11/11 resident dermatologists contacted, participated in the study.<br><br>4/6 attending dermatologists contacted, participated in the study.<br><br>Participants were randomised to 1 of 6 different sequences of methods, to control for 'order of method' effect.<br><br>For the 25 lesions viewed on patients, histological confirmation was obtained.<br><br>Study lesions included diagnostically difficult lesions. | 3 + |
| (Harvey 1997) | To discuss findings of the study by Whited et al. (1997, see below). | Expert opinion. | **Author is based in the UK** | | Author states:<br>• The diagnostic ability of dermatologists arises through years of additional training<br>• The predictive value of a diagnosis of skin cancer by dermatologists is usually between 50% and 60%<br>• Possible bias arises through the use of patient participants who may already be known dermatologists.<br>• Screening for skin cancer should be experimentally evaluated. | Response in ACP journal club to study by Whited et al. (1997, see below). | 4 |
| (Julian 1999) | To determine the nature and frequency of skin disease seen in general practice. | Retrospective case series analysis of data collected over a 5 year period at a | Single GP with an interest in dermatology. | Proportion of patients with skin disease of various types, listed by | 21% of all patients seen at the practice had skin disease, increasing from 16% in 1989 to 37% in 1994. | Useful to this research question only in terms of providing an estimate of the numbers of SCC, BCC and | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | general practice in Cornwall. | Case mix: 11,191 patients seen at a single practice over a 5 year period of which 2386 presented with skin disease.<br><br>**UK** | specific condition, including NMSC. | Of 2386 patients with skin disease, 74 had skin cancer (3%):<br><br>Melanoma: 2 (2.7% of skin cancers)<br>SCC 10 (13.5% of skin cancers)<br>BCC 62 (83.8% of skin cancers).<br><br>All malignant tumours were treated at the practice and all surgical specimens were sent for histological confirmation. | melanoma observed in a UK general practice with a GP with dermatological interest.<br><br>Does not measure the diagnostic performance of the GP compared with the histological finding. | |
| (Lathlean 1999) | To record the relative frequency of different skin tumours in an Adelaide general practice and compare these with rates published elsewhere.<br><br>To record clinical accuracy of diagnosis, infection rates and completeness of excision. | Prospective case series study undertaken at a single general practice. | 1 GP in Adelaide who performed excisions on 369 patients presenting with skin lesions.<br><br>Patient age range was 20 – 69 years.<br><br>**Australia** | Study describes incidence and age distribution of NMSC.<br><br>Diagnostic accuracy of single GP with 5 years experience of excising skin lesions.<br><br>Completeness of excision. | Histologically, BCC accounted for 113 of all 369 lesions (30.6%), SCC 80 (21.7%). Solar keratoses were the commonest benign lesion accounting for 40 (21.7%) of all lesions.<br><br>NMSC (BCC plus SCC) was correctly diagnosed in 120/155 of histologically confirmed NMSC tumours, equating a sensitivity for clinical diagnosis of 77%.<br><br>False negative rate for NMSC by clinical diagnosis was 9/155 = 5.8%. | Patients and lesions reported interchangeably, therefore 1 lesion per patient.<br><br>Histological diagnosis reported as reference standard, although this data is also reported as recorded for only two years of the five year study period. It is uncertain whether all lesions were histologically reported.<br><br>Sensitivity and false negative rate calculated from data reported in study. | 3 - |
| (McWilliam *et al.* 1991) | To evaluate and appraise skin biopsies performed by GPs and compare their performance with that of hospital doctors. | Retrospective analysis of histology records between 1989 and 1991.<br><br>Examination of computer records for the years 1984 – 1989. | Records of 292 skin biopsy specimens obtained by GPs and 324 specimens obtained by hospital doctors.<br><br>Results represent specimens of all skin biopsy samples, including skin cancer and benign skin lesions.<br><br>**UK** | Clinical and pathological diagnoses and completeness of excision.<br><br>Quality of information provided on request cards, by assigning a score of poor, average or good. | The range of diagnoses was similar among hospital and general practitioner cases, although malignancy was commoner in hospital cases (63/324 (19%) v 14/292 (5%) in general practitioner cases; chi 2 = 28, p < 0.00001).<br><br>The quality of clinical information given on request forms was similar between groups.<br><br>Accuracy of clinical recognition of lesions was significantly less among GPs compared to hospital doctors (p < 0.00001).<br><br>In 41% of cases there was good agreement between GPs clinical diagnosis and histopathological findings; the figure for hospital cases was 62%.<br><br>Authors conclude that the performance of skin biopsy by GPs could be | Total numbers are used rather than samples, although hospital cases of specimens from lesions >3.0 cm in diameter excluded, to optimise comparability with samples from primary care.<br><br>Very little information provided by lesion type. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | improved and that all skin specimens should be sent for histological examination. | | |
| (Morrison *et al.* 2001) | To compare the diagnoses of GPs and dermatologists over a selected period in patients with a possible diagnosis of skin cancer. | Case series. | 493 patients referred to a Skin Cancer Screening Clinic by their GP for diagnosis and / or treatment of lesions suspicious of skin cancer.<br><br>Comparison is made between GPs (number not reported) and either of two dermatologists at the screening centre.<br><br>**Ireland** | Agreement of clinical diagnosis between GP and dermatologist for lesions with no histological information.<br><br>Proportion of correct diagnoses by GPs and dermatologists for histologically confirmed lesions. | Agreement between GP and dermatologist for *clinically diagnosed lesions* was:<br><br>Melanocytic nevi 97%<br>Seborrhoeic keratoses 33%<br>Actinic keratoses 7%<br>SCC 0% (n=2)<br>Benign lesions 25%<br><br>For histologically confirmed lesions:<br><br>For benign melanocytic nevi, dermatologists' clinical diagnoses were correct in 94% of cases and GPs in 90% of cases. These values were, respectively, 95% and 40% for BCC, 77% and 22% for SCC and 75% and 25% for melanoma.<br><br>Author concludes that there is a need to educate GPs in the recognition of skin lesions suspicious of cancer. | No statistical test to measure significance of observed differences.<br><br>GP numbers not reported.<br><br>Small sample of dermatologists (n = 2).<br><br>Study does not capture skin lesions managed in primary care with no dermatologist input. | 3 |
| (Offidani *et al.* 2002) | To assess the ability of general practitioners (GPs) in the early diagnosis of skin cancers, their correct differential diagnosis of benign lesions and their accuracy in the choice of the treatment. | Cross sectional survey of diagnostic ability of GPs for skin cancer.<br><br>GPS received four images of skin lesions plus seven clinical case descriptions and a multiple choice questionnaire. | 288 responding GPs out of 625 GPs who were sent the questionnaire.<br><br>**Italy** | GPs' diagnostic ability for melanoma, SCC, BCC and seborrhoeic keratoses.<br><br>GPs' ability to state correct therapeutic action for above lesions.<br><br>Self reported opinion on ability to diagnose skin cancers. | A mean of 115 patients per GP made consultations for dermatological conditions per year.<br><br>1% of GPS reported 'good' confidence in their diagnostic ability. 31% reported 'slight' confidence and confidence was significantly higher according to a greater number of dermatological cases seen per year.<br><br>103 (36%) GPs correctly diagnosed seborrhoeic keratoses.<br>118 (41%) GPs accurately recognised BCC and proposed correct intervention.<br>153 (53%) GPs correctly diagnosed SCC.<br>262 (91%) of GPs correctly identified melanoma.<br><br>Authors conclude: Many GPs are not confident in their ability to recognise the most common skin cancers, and knowledge deficiencies were identified. | The sample of GPs had been practicing for approximately 17 years on average. Younger GPs appeared less likely to respond compared to middle aged GPs whereas the oldest GPs were reported as 'scarcely interested'.<br><br>The small number of images viewed permits a simple assessment of diagnostic ability of 'classic' and fairly distinct lesions.<br><br>Response rate is low: 288/625 (46%). | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Raasch 1999) | To describe the diagnosis made and subsequent clinical management decisions of GPs with regard to NMSC. | Prospective case series. | 61 GPs who provided detailed data for 418 patients, presenting with a total of 1355 skin lesions.<br><br>**Australia** | Diagnostic accuracy of GPs compared with histological diagnosis.<br><br>GPs' reported actions for treatment, referral or biopsy of lesions, with analysis by GPs' reported certainty of diagnosis. | For lesions histologically confirmed by local pathologists as BCC or SCC, the clinical diagnosis of the GP was correct in 69.1% of cases (95% CI 62.5-75.7%) i.e. BCC 73.5% (95% CI 64-83%), SCC 62.2% (95% CI 57-68%). | Histopathology provided gold standard.<br><br>Histology was available for 419/1355 (30.9%) of lesions.<br><br>Proportion of NMSC histologically proven was compared with that observed in routine practice and found statistically to be similar.<br><br>Histological cases of SCC were reviewed by a further, external consultant dermatopathologist.<br><br>GPs self reported that median 85% (range 50-99%) of cases were recorded in the study.<br><br>GP participants differed to non participants only in gender, with women over represented. | 3 - |
| (Raasch *et al.* 2000) | To test whether auditing and providing feedback (on diagnostic and management ability) to primary care physicians improves their performance. | RCT undertaken over 9 months.<br><br>Doctors underwent Pre and post testing either side of feedback intervention.<br><br>Intervention (n=23) doctors provided with audit feedback on their performance.<br><br>Control (n=23) doctors audited but not provided with feedback until after the study had concluded. | 46 primary care physicians, audited on the treatment of 1366 patients and 1416 skin lesions.<br><br>Physicians had to work 3 or more sessions per week in primary care to be eligible.<br><br>**Australia** | Mean no. of correct clinical diagnoses.<br><br>Mean certainty of diagnosis score.<br><br>Mean no. of inadequate excisions per doctor.<br><br>Mean no. of pathology results with no clinical diagnosis recorded.<br><br>PPV and Sensitivity with regard to malignant and benign lesions. | There was no significant change within or between groups for mean proportion of correct clinical diagnoses per doctor.<br><br>Both intervention and control groups significantly improved for certainty of diagnosis score and mean no. of inadequate excisions, but with no significant difference between groups.<br><br>The intervention group showed a significantly greater improvement than the control group for the mean no. of pathology requests submitted without clinical diagnoses.<br><br>There were no significant differences between groups for PPV of diagnoses.<br><br>The only significant difference for sensitivity of diagnosis was for benign lesions only, at pre-test stage only, between intervention and control groups.<br><br>Authors conclude that patient factors | Of 91 eligible doctors, 46 were randomised.<br><br>Doctor groups similar at outset but for number of doctors per practice (more in control).<br><br>Patients treated in each group differed: more young patients, female patients and those with histologically or clinically malignant diagnoses were seen in the intervention group.<br><br>3 doctors in the control group dropped out or provided no data. This figure for the intervention group was 2.<br><br>Power calculation based upon 356 patient consultations.<br><br>Doctors consented to trial participation but were not told their randomised arm. Doctors | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | confounded the study such that very little difference was observed between randomised groups. | knew of audit since they obtained patient consent for review of records by the researcher.<br><br>Possible Hawthorne effect since all doctors knew of audit. Similarly if randomised individually (not clearly reported) doctors within the same practice could discuss the trial. | |
| (Rodriguez *et al.* 2000) | To evaluate the concordance and diagnostic validity between hospital dermatologists and GPs of a single health administration area within Madrid. | Retrospective analysis of clinical histories. | 564 patients referred from primary care to hospital dermatology department.<br><br>**Spain** | Sensitivity, specificity and predictive values.<br><br>Agreement assessed by kappa statistic. | 70 BCCs and 139 melanocytic naevi were reported.<br><br>Sensitivity of dermatologists in the diagnosis of BCC was 91.4% and in GPs 41.4%.<br><br>Sensitivity of dermatologists was 96.4% for melanocytic naevi and in GPs 56.4% ($p < 0.05$).<br><br>Specificity of dermatologists was 88.5% for BCC and in GPs 75.4%.<br><br>Specificity of dermatologists was 96.4% for melanocytic naevi and in GPs 70.9% ($p < 0.05$).<br><br>Authors conclude that concordance of diagnoses was low and that dermatologists had greater sensitivity and specificity than GPs. | Study published in Spanish. Abstract only read by reviewer.<br><br>Power calculation performed to estimate necessary sample size (561 subjects).<br><br>No data reported for skin lesions other than BCC and melanocytic naevi. | 3 |
| (Schofield *et al.* 1993) | To report on the experience of a histopathology department in South West Hertfordshire with regard to skin surgery specimens received from primary care after introduction of the UK NHS GPs' contract. | Retrospective audit of 2 years activity preceding the introduction of the contract compared with similar data for a 12 month period after the introduction of the contract, plus additional data from histopathology reports. | 1684 skin surgery specimens received over a three year period by a histopathology department serving 125 GPs on the minor surgery list.<br><br>Patient population served is 244 000 people.<br><br>**UK** | Numbers of specimens received.<br><br>GPs' diagnostic ability.<br><br>Adequacy of excision performed by GPs.<br><br>Follow-up pattern. | **Over the three year period:**<br><br>983 specimens were received in the 12months post contract compared with 350 during 1988-1989 and 351 during 1989-1990.<br><br>Over the three years specimens received included a total of 3 melanomas, 19 BCCs and 15 SCC / Bowens disease tumours.<br><br>**In the post contract 12 month period:**<br><br>GPs accurately diagnosed the skin cancer type in 2/14 cases (sensitivity | 92% of GPs in the region were on the minor surgical list. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | 14.3% compared with histology).<br><br>Of 14 patients with skin malignancy, one received no follow-up (1 patient with completely excised SCC), 6 patients (with SCC, Bowens disease or BCC) received GP follow-up and 7 were referred to specialist follow-up. | | |
| (Whited *et al.* 1997) | To compare diagnostic ability of primary care physicians and dermatologists for malignant and non malignant skin lesions. | Cross sectional study comparing diagnostic ability between a sample of primary care physicians and a sample of dermatologists. | 12 primary care physicians and 8 dermatologists.<br><br>A convenience sample of 190 dermatology or general medicine patients (white men aged ≥40 years) were recruited for skin examination.<br><br>**US** | Examining doctors' ability to identify possible malignant skin tumours warranting biopsy and actinic keratoses.<br><br>Analysis performed by patient for referral by primary care physicians and otherwise by lesion.<br><br>Sensitivity, specificity and likelihood ratio (LR) reported for primary care physicians' diagnostic ability.<br><br>Kappa statistic measures agreement compared with chance, where:<br><br>K = -1 perfect disagreement<br>K = 0 chance agreement<br>K = 1 perfect agreement. | A total of 883 lesions were identified.<br><br>Agreement between primary care physicians and dermatologists was moderate as to whether a patient had single actinic keratosis (kappa, 0.36; 95% confidence interval [CI] 0.22-0.50), multiple actinic keratoses (kappa, 0.48; 95% CI, 0.34-0.61), or skin cancer (kappa, 0.48; 95% CI, 0.34-0.62). Agreement decreased when individual lesions were the unit of analysis.<br><br>When the patient was the unit of analysis, primary care clinicians identified the presence of skin cancer with a sensitivity of 57% (95% CI, 44%-68%), specificity of 88% (95% CI, 81%-93%), positive likelihood ratio of 4.9 (95% CI, 3.0-8.3), and negative likelihood ratio of 0.48 (95% CI, 0.350.63).<br><br>When the lesion was the unit of analysis the sensitivity of primary care physicians was 38% (95% CI, 29%-47%), the specificity was 95% (95% CI, 93%-96%), the positive likelihood ratio was 7.1 (95% CI, 4.8-10.3), and the negative likelihood ratio was 0.66 (95% CI, 0.56-0.75).<br><br>The authors concluded that examinations performed by primary care clinicians for diagnosing skin cancer lacked sensitivity. Without improved diagnostic skills, primary care clinicians' examinations may be ineffective as a screening test. | Possible limited applicability to UK since primary care physicians included 'general medicine fellows' and 'attending physicians'.<br><br>Primary care physicians performed examination first, since the dermatologists treated some patients during their consultation.<br><br>Dermatologist examiners blind to primary care physicians' diagnoses.<br><br>Examiners were not asked to predict the pathological type of skin malignancy.<br><br>Dermatologists' diagnoses used as reference standard for malignancy. Pathological diagnosis recorded in patients in whom dermatologists diagnosed malignancy.<br><br>Primary care physicians varied in terms of working arrangements and dermatological experience.<br><br>8 additional patients were excluded from the analysis due to failure to attend the second examination or improper data collection. | 3 ++ |
| (Williams *et al.* 1991) | To investigate whether GPs submitted more skin lesion biopsy samples for histopathology following | Retrospective case series.<br><br>Histopathology | 338 skin lesion specimens, from a total of 357 specimens were | Proportion of skin specimens that were from histologically | Over the study period 26/233 (11.2%) of the skin specimens were from histologically malignant lesions, as follows: | Small number of skin cancer lesions.<br><br>Study is only able to estimate | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | the introduction of a new contract in 1990. | department database was interrogated to review skin biopsies sent from primary care over a 1 year period. | received from 60 general practices, with 100 GPs.<br><br>**UK** | malignant lesions in 1989 compared with 1990. | BCC (14)<br>SCC (8)<br>Melanoma (4)<br><br>All skin specimens were excision biopsies.<br><br>6 (2.6%) of the skin specimens were from histologically malignant lesions in 1989 compared with 20 (5.9%) in 1990 (p = 0.024).<br><br>**GP clinical diagnosis of skin cancer:**<br><br>For NMSC GP sensitivity was 7/22 = 31.8%, for strictly correct clinical diagnosis of SCC or BCC.<br><br>For NMSC, GP sensitivity was 13/22 = 59.1% for suspicion of malignancy.<br><br>GPs correctly diagnosed or suspected melanoma in 2/4 histologically proven melanoma tumours.<br><br>The authors concluded that the benefits of GPs excising skin cancer tumours early are debated, and that it is essential that GPs who undertake minor surgery are adequately trained and that all biopsy samples are submitted for histological examination. | GP performance based upon samples sent for histological evaluation.<br><br>Sensitivity values were not reported in study, but the information was available for inclusion here. | |

**The question**

*What is the ability of General Practitioners to treat NMSC?*

**The nature of the evidence**

Thirteen studies were identified as follows:

- Eleven observational studies, three of good quality, two of fair quality and six of poor quality
- One service guideline of good quality
- One expert review of good quality.

Six studies are from the UK, three studies are from Australia, two are form New Zealand and one study is from the US. Applicability to the UK is reasonable, but limited.

Six studies are either samples of GPs or report on the experience of GP practices. Six studies report from the perspective of the referral centre, usually pathology departments. All studies address patients who underwent surgery for NMSC.

**Summary of the supporting evidence for the recommendations**

**Observational studies have measured the incomplete excision rate of NMSC tumours by GPs as a measure of performance, although it should be noted that often the studies have analysed small numbers of skin cancer lesions that were excised in primary care and the quality of the studies is variable. Overall, patients with NMSC treated in secondary care by specialists appear to receive a higher rate of adequate excision than those treated in primary care.**

**The rate of incomplete excision of NMSC tumours by GPs is reported within the studies identified as between 9.9% and 31.6%. This range for doctors in secondary care is 8% to 12%. The incomplete excision rate by GPs for BCC tumours from the identified studies has range 11.3% to 27.6% and for SCC, 5.8% to 35.7%. Where studies report incomplete excision rates for 'skin cancer', the rate for GPs has range 10% to 80% and this range for secondary care is 10% to 11%. One audit from within the UK demonstrated that where GPs work to an agreed protocol dealing only with low risk lesions, the incomplete excision rate for BCC was 7.3% and for SCC 13.7%, which was reported as similar to the rates observed within secondary care.**

**Observational study evidence is also suggestive that GPs manage a high proportion of clinically diagnosed BCC and SCC by excision or biopsy, independent of certainty of diagnosis. The same level of evidence is suggestive of a lack of a consistent pattern of management with regard to which lesions should be managed within primary care and which speciality to refer patients to. Expert review evidence is supportive of multidisciplinary management of patients with high risk NMSC.**

**UK guidelines for plastic surgery services in the NHS strongly support both pre and post graduate education of GPs in the recognition of skin lesions, and recommend adherence to nationally set standards and that GPs be given adequate, ongoing mentorship for dermatological work.**

- Service Guidance produced by the British Association of Plastic Surgeons and NHS Modernisation Agency (2005) recommends that the education and on-going post graduate education of GPs should ideally include emphasis on the differential diagnosis and management of skin lesions in order to develop the necessary confidence in differentiating benign from malignant skin conditions.

- The prospective case series study by Corwin, Munn and Nicholls (1997) found that the malignant to benign ratio in 303 excised lesions submitted for histology by GPs was 61/242 i.e. approximately 1:4. Incomplete excision rates were: BCC: 27.6%, SCC: 35.7% and NMSC: 31.6%.

- The retrospective audit by El-Dar, Davies, and Roberts (2004) studied GPs who were trained as experts in the treatment of patients with NMSC, working to a protocol and found the incomplete excision rate to be 7.3% for BCC and 13.7% for SCC.

- The retrospective audit by Hillan, Johnson, and Morton (1991) found the incomplete excision rate for skin cancer lesions treated by GPs to be 10%, compared to 11% for lesions treated in secondary care.

- The prospective case series study by Lathlean (1999) demonstrated that the incomplete excision rate by a single Australian GP for skin lesions including NMSC and benign lesions was 13%.

- The expert review by Martinez and Otley (2001) reported that the precise degree of training required for physicians to safely treat patients with low risk NMSC has not

been universally established and stated the importance of specialist, multidisciplinary management of patients with high risk NMSC.

- The retrospective case series study by McWilliam et al. (1991) found the incomplete excision rate of malignant skin lesions to be 80% for GPs and 10% for hospital surgeons.

- The prospective case series study by Raasch (1999) found that GPs reported managing 71.2% (95% CI, 65.6-76.7%) of clinically diagnosed BCC and 90.2% (95% CI, 85.6-94.9) of SCC by excision or biopsy and that certainty of diagnosis made no significant difference as to whether GPs chose to treat BCC or SCC by excision.

- The small, interrupted time series study by Reid (2000) found that the incomplete excision rate for NMSC by a single, Australian GP was 9.9% (11.3% for BCC and 5.8% for SCC). Deeper tumours located on the head and neck were more likely to be incompletely excised.

- The retrospective audit by Schofield, O'Neill, and Tatnall (1993) found the GP incomplete excision rate for skin tumours (mostly NMSC) to be 33.3%. Of 14 patients with skin malignancy, 7 were referred to specialist follow-up.

- The retrospective case series study Shapley (2005) of a single GP practice in which 1 GP performed all skin surgery found that of 80 skin cancer lesions operated on in primary care, 7 recurred (1 melanoma, 1 SCC and 5 BCCs) with the recurrence rate for BCC reported as 14.7%. There was no consistent pattern of management with regard to which lesions should be managed within primary care, which speciality to refer patients to or frequency of follow-up.

- The retrospective case series by Talbot and Hitchcock (2004) found that of 1833 NMSC lesions excised, the incomplete excision rate for GPs was 16%, for consultant surgeons 12% and for surgical registrars 8%. These values were found to be statistically significantly different.

- The retrospective case series study by Williams, Burdge and Jones (1991) found that after the introduction of a new GP contract in 1990, the rate of excision biopsy of malignant lesions in primary care significantly rose from 2.6% of all specimens received by a pathology department to 5.9%.

# EVIDENCE TABLE 3.4

## *What is the ability of General Practitioners to treat NMSC?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (British Association of Plastic Surgeons & NHS Modernisation Agency 2005) | To provide guidance for patient-centred models of care in the overlap areas between Plastic, Reconstructive and Aesthetic Surgery and Dermatology. | Service Guideline. | Patients with skin conditions for whom Plastic Surgeons have an input to care.<br><br>**UK** | Recommendations for practice. | **Recommendations**<br><br>**GPs:**<br><br>The education and on-going post graduate education of GPs should ideally include emphasis on the differential diagnosis and management of skin lesions in order to develop the necessary confidence in differentiating benign from malignant skin conditions. This would facilitate the early diagnosis and treatment of skin cancer.<br><br>**Practitioners in skin surgery in primary care:**<br><br>Practitioners in skin surgery in primary care should:<br><br>● Be trained appropriately to nationally agreed standards and guidance.<br><br>● Have suitable mentors (these would be individuals with appropriate, designated, surgical skills).<br><br>● Comply with the NICE Skin Cancer Guidance particularly in relation to involvement in multidisciplinary working.<br><br>● Retrain /revalidate as appropriate to both nationally and locally agreed frameworks.<br><br>● Utilise appropriate equipment and facilities (National Care standards). | Part of a larger strategy for the planning and delivery of patient-centred Plastic Surgery services within the NHS, titled, *Action On Plastic Surgery (AOPS) Programme* .<br><br>AOPS started in 2002 and has put in place 19 AOPS Pilot Site Projects in England and Wales, (18 funded by the Department of Health (England) and one funded by the Welsh Assembly.<br><br>Associated work has been undertaken in Scotland. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Corwin *et al.* 1997) | To evaluate skin surgery undertaken by GPs by review of histology samples sent to a single pathology department. | Prospective case series of samples received from a random sample of GPs who performed surgery, studied over a 5 month period. | 28 participating GPs.<br><br>**New Zealand** | Completeness of excision.<br><br>Clinical diagnostic performance. | Audit forms were completed by participating GPs for 214 (70%) of 303 specimens submitted.<br><br>Of the 303 lesions, histological diagnosis was:<br>BCC 29<br>SCC 28<br>Melanoma 3<br>Cutaneous lymphoma 1<br><br>Malignant: benign ratio in the 303 lesions submitted was 61/242 i.e. approximately 1:4.<br><br>Incomplete excision rates were:<br>BCC 8/29 (27.6%)<br>SCC 10/28 (35.7%)<br>NMSC 18/57 (31.6%)<br>Melanoma 1/3 (33.3%)<br><br>Authors conclude that GPs in New Zealand undertake more skin surgery and to a higher standard than their counterparts in the UK, yet there is room for improvement. | In addition to the 303 specimens received, 28 patients were identified as referred to specialists for treatment (likely to be an under estimate).<br><br>Sensitivity and specificity calculated from Table 1 in paper.<br><br>Lesions that underwent diagnostic biopsy were not counted as incompletely excised.<br><br>Of 29 GPs randomly sampled, 1 declined to participate.<br><br>Histology used as gold standard. | 3 ++ |
| (El-Dar *et al.* 2004) | To investigate whether the treatment of patients with NMSC by expert GP clinics working to a protocol agreed by the local dermatology department was of the same standard as that traditionally provided by dermatology or plastic surgery departments. | Retrospective audit. | 9 GPs in West Wales, expert in treatment of patients with NMSC.<br><br>1892 patients with NMSC were seen over the audit period.<br><br>**UK** | Incomplete excision rate of NMSC, as reported by the GPs via postal survey.<br><br>Patient satisfaction via survey. | 20.1% of patients seen in primary care were referred on to secondary care.<br><br>The incomplete excision rate by the expert GP clinics was 7.3% for BCCs and 13.7% for SCC.<br><br>The incomplete excision rate for BCCs by the expert GP clinics compared favourably with data published in the literature.<br><br>Patient satisfaction of treatment by the expert GP clinics was very high.<br><br>Authors concluded that the treatment of NMSC in expert GP clinics may reduce secondary care referrals by up to 80%, significantly reducing the workload of hospital dermatology departments. Patient satisfaction with the clinics is high, and the provision of primary care expert GP clinics may be one future strategy that could be implemented to | Evidence grade assigned based upon poster abstract alone.<br><br>Incomplete excision rates were reported by GPs rather than by histology department. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | help to deal with the increasing demand for treatment of patients with NMSC. | | |
| (Hillan *et al.* 1991). | To investigate whether the GP contract had resulted in increased numbers of tissue samples sent by GPs for histology findings and whether misdiagnosis of skin lesions occurs. | Retrospective audit of tissue specimens sent from primary care to a single pathology department between the years 1987 – 1991.<br><br>For the last year of study comparison was made with 106 samples received from secondary care day surgery patients matched for age and sex. | 149 skin specimens from patients who underwent skin surgery performed by a total of 22 GPs.<br><br>**UK** | Adequacy of clinical information.<br><br>Patient details.<br><br>Tissue sample details.<br><br>Completeness of excision. | Specimens included melanoma, SCC (Bowens disease) and BCC.<br><br>**GP specimens:**<br>16% of samples were in the wrong fixative.<br><br>Duration of lesion was recorded in 15% of cases.<br><br>Clinical details were otherwise complete in 67% of cases.<br><br>10% of lesions were incompletely excised.<br><br>**Day surgery specimens:**<br>The duration of the lesion was recorded in 12% of samples.<br><br>Clinical details were otherwise complete in 94% of cases.<br><br>11% of lesions were incompletely excised.<br><br>The authors concluded that there was little evidence for misdiagnosis by GPs and that incomplete excision was similar between primary and secondary care. | Study aims not clearly stated<br><br>Since 59% of specimens were from four GPs and 40% were from a single practice, this may weaken the extent to which the observed group of 22 GPs are representative of widespread practice.<br><br>No statistical method employed to assess whether outcomes differed significantly between groups.<br><br>Day surgery cases, although matched for age and sex, may have systematically differed from patients treated in primary care.<br><br>Study is only able to estimate GP performance based upon samples sent for histological evaluation. | 3 - |
| (Lathlean 1999) | To record the relative frequency of different skin tumours in an Adelaide general practice and compare these with rates published elsewhere.<br><br>To record clinical accuracy of diagnosis, infection rates and completeness of excision. | Prospective case series study undertaken at a single general practice. | 1 GP in Adelaide who performed excisions on 369 patients presenting with skin lesions.<br><br>Patient age range was 20 – 69 years.<br><br>**Australia** | Study describes incidence and age distribution of NMSC.<br><br>Diagnostic accuracy of single GP with 5 years experience of excising skin lesions.<br><br>Completeness of excision. | Histologically, BCC accounted for 113 of all 369 lesions (30.6%), SCC 80 (21.7%). Solar keratoses were the commonest benign lesion accounting for 40 (21.7%) of all lesions.<br><br>Completeness of excision was achieved in 321/369 (87%) of lesions (including benign lesions). | Histological diagnosis reported as reference standard, although this data is also reported as recorded for only two years of the five year study period. It is uncertain whether all lesions were histologically reported. | 3 - |
| (Martinez & Otley 2001) | To review evidence and draw recommendations | Expert review (45 references). | Patients with skin cancer. | Recommendations for practice | The authors note that the precise degree of training required to safely | No description of methodology. | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | for practitioners in the treatment of melanoma and NMSC. | | **Review undertaken in US** | including treatment algorithms. | treat patients with low risk NMSC has not been universally established.<br><br>Patients with high risk NMSC require management by specialists from disciplined including dermatology, Mohs micrographic surgery, radiotherapy and surgical oncology. | | |
| (McWilliam *et al.* 1991) | To evaluate and appraise skin biopsies performed by GPs and compare their performance with that of hospital doctors. | Retrospective analysis of histology records between 1989 and 1991.<br><br>Examination of computer records for the years 1984 – 1989. | Records of 292 skin biopsy specimens obtained by GPs and 324 specimens obtained by hospital doctors.<br><br>Results represent specimens of all skin biopsy samples, including skin cancer and benign skin lesions.<br><br>**UK** | Change in the number of skin biopsy samples received over the study period.<br><br>Clinical and pathological diagnoses and completeness of excision.<br><br>Quality of information provided on request cards, by assigning a score of poor, average or good. | The number of specimens received from surgeons and GPs increased over the study period of 1984-1990; the proportion of specimens from GPs rose from 17/1268 (1.3%) in 1984 to 201/2387 (8.7%) in 1990.<br><br>The range of diagnoses was similar among hospital and general practitioner cases, although malignancy was commoner in hospital cases (63/324 (19%) v 14/292 (5%) in general practitioner cases; chi 2 = 28, p < 0.00001).<br><br>The quality of clinical information given on request forms was similar between groups.<br><br>Completeness of excision was less common among general practitioners than hospital surgeons (150/233 (3/15 malignant) v 195/232 (57/63) p < 0.00001).<br><br>Authors conclude that the performance of skin biopsy by GPs could be improved and that all skin specimens should be sent for histological examination. | Total numbers are used rather than samples, although hospital cases of specimens from lesions >3.0 cm in diameter excluded, to optimise comparability with samples from primary care.<br><br>Very little information provided by lesion type. | 3 + |
| (Raasch 1999) | To describe the diagnosis made and subsequent clinical management decisions of GPs with regard to NMSC. | Prospective case series. | 61 GPs who provided detailed data for 418 patients, presenting with a total of 1355 skin lesions.<br><br>**Australia** | Diagnostic accuracy of GPs compared with histological diagnosis.<br><br>GPs' reported actions for treatment, referral or biopsy of lesions, with analysis by GPs' reported certainty | The GPs reported managing 71.2% (95% CI, 65.6-76.7%) of clinically diagnosed BCC and 90.2% (95% CI, 85.6-94.9) of SCC by excision or biopsy.<br><br>If more certain of the diagnosis of solar keratosis GPs were likely to treat without obtaining histology and if less certain they were likely to excise or biopsy (p = < 0.0001).<br><br>Certainty of diagnosis made no | Histopathology provided gold standard.<br><br>Histology was available for 419/1355 (30.9%) of lesions.<br><br>Proportion of NMSC histologically proven was compared with that observed in routine practice and found statistically to be similar.<br><br>Histological cases of SCC | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | of diagnosis. | significant difference as to whether GPs chose to treat BCC or SCC by excision. | were reviewed by a further, external consultant dermatopathologist.<br><br>GPs self reported that median 85% (range 50-99%) of cases were recorded in the study.<br><br>GP participants differed to non participants only in gender, with women over represented. | |
| (Reid 2000) | To develop a set of predictors for incomplete excision of NMSC and to determine their effect when used in general practice, in reducing the incomplete excision rate for NMSC . | Interrupted time series consisting of:<br><br>Retrospective audit of 6 years (1992-1998) of practice by a single GP, followed by:<br><br>Prospective audit over 18 months (April 1998-September 1999) by the same GP, with knowledge of predictive factors for incomplete excision. | Single GP who treated:<br><br>464 patients with NMSC in the retrospective period.<br><br>173 patients with NMSC in the prospective period.<br><br>**Australia** | Incomplete excision rate. | **Retrospective study:**<br>Of the NMSC tumours excised, 9.9% (11.3% of BCC and 5.8% of SCC) were incompletely excised. For NMSC, deeper tumours located on the head and neck were more likely to be incompletely excised.<br><br>**Prospective study where GP used predictive criteria to commit more surgery time to difficult tumours:**<br>The proportion of NMSC incompletely excised fell to 4.6% ($p < 0.05$, breakdown by tumour type: BCC 5.4%, SCC 3.2%) but tumours on the head and neck continued to be more likely to be incompletely excised. | Single GP is the study participant and researcher.<br><br>Small numbers of lesions especially in prospective audit.<br><br>Data in retrospective study do not clearly indicate how all of the predictive criteria were derived. | 3 - |
| (Schofield *et al.* 1993) | To report on the experience of a histopathology department in South West Hertfordshire with regard to skin surgery specimens received from primary care after introduction of the UK NHS GPs' contract. | Retrospective audit of 2 years activity preceding the introduction of the contract compared with similar data for a 12 month period after the introduction of the contract, plus additional data from histopathology reports. | 1684 skin surgery specimens received over a three year period by a histopathology department serving 125 GPs on the minor surgery list.<br><br>Patient population served is 244 000 people.<br><br>**UK** | Numbers of specimens received.<br><br>GPs' diagnostic ability.<br><br>Adequacy of excision performed by GPs.<br><br>Follow-up pattern. | **Over the three year period:**<br><br>983 specimens were received in the 12months post contract compared with 350 during 1988-1989 and 351 during 1989-1990.<br><br>Over the three years specimens received included a total of 3 melanomas, 19 BCCs and 15 SCC / Bowens disease tumours.<br><br>**In the post contract 12 month period:**<br><br>In 8/12 (66.7%) primary skin tumours the lesion was completely excised.<br><br>Complete excision rate was 3/5 BCCs, 2/3 SCC and 2/3 Bowens disease.<br><br>Of 14 patients with skin malignancy, | 92% of GPs in the region were on the minor surgical list. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | one received no follow-up (1 patient with completely excised SCC), 6 patients (with SCC, Bowens disease or BCC) received GP follow-up and 7 were referred to specialist follow-up. | | |
| (Shapley 2005) | To report the management of malignant skin conditions that occurred in a UK general practice during the 10 years following the introduction of the 1990 GP contract. | Large, retrospective case series study by interrogating data routinely added to primary care / secondary care databases. | Single GP practice in which 1 GP performed all skin surgery.<br><br>Practice served approximately 10,000 patients, from whom 136 skin malignancies were reviewed over a 10 year period, representing 101 patients.<br><br>**UK** | Practice based estimate of incidence of skin malignancy.<br><br>Proportions of malignancies treated in primary care.<br><br>Recurrence rates.<br><br>Referral patterns. | **Malignancies managed in primary care:**<br>Of 136 malignant lesions identified, 80 (58.8%) were initially operated on in primary care and 56 (41.2%) were initially operated on in secondary care. 43.4% of all malignancies were wholly managed in primary care.<br><br>6/10 (60%) melanoma tumours were initially operated on in primary care.<br><br>61/105 (58.1%) BCC tumours were initially operated ion in primary care.<br><br>12/18 (66.7%) SCC tumours were initially operated on in primary care.<br><br>**Recurrence**:<br><br>1 melanoma, 1 SCC and 5 BCC tumours initially managed in primary care recurred, representing 1 death from SCC.<br><br>Recurrence rate for BCC was 14.7%.<br><br>**Referral patterns:**<br><br>There was no consistent pattern of management with regard to which lesions should be managed within primary care, which speciality to refer patients to or frequency of follow-up. | Experience of GP performing all surgery is not reported.<br><br>Median follow-up for recurrences was 5.8 years (range 0.6 – 12.6).<br><br>BCC recurrence rate calculated by 'strict' method; described in another paper.<br><br>Practice studied likely to be highly organised in terms of management of skin lesions; more so than on average. | 3 |
| (Talbot & Hitchcock 2004) | To investigate factors associated with pathologically reported incomplete primary excision of SCC and BCC. | Retrospective review of histology reports with review of operation notes for all hospital in patients during the period 1 January through 30 June 2001. | 1320 patients with primary excised SCC or BCC in a single hospital catchment area. Average age was 70 years and 61% were male.<br><br>Population had larger numbers of elderly people and | Incomplete excision rate of SCC and BCC according to surgical training, site of lesion, pathology, and location of positive margin involvement. | 1833 NMSC lesions were excised from the 1320 patients:<br><br>1126 (61%) BCC<br>705 (39%) SCC<br>2 basosquamous carcinomas<br><br>257 (14%) tumours were reported as incompletely excised. There was no difference in rates of positive margin involvement for gender or histology. | 16 histology reports failed to state completeness of excision and were excluded from the analysis.<br><br>No tumour subtype analysis was possible.<br><br>Presumably 10% of incomplete excision involved both margins? | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | Maori people than the New Zealand average.<br><br>**New Zealand** | | *Proportionately*, excisions from the nose and ear revealed the highest incomplete excision rates (28% and 31% respectively)<br><br>General practitioners excised 1015 lesions, with a 16% incomplete excision rate. Consultant surgeons excised 695 lesions, with a 12% incomplete excision rate. Surgical registrars excised 123 lesions, incompletely excising 8%. These data are statistically significant ($p < 0.01$).<br><br>Tumour was most often found at lateral (73%) than deep (13%) margins.<br><br>Authors conclude: The incidence of NMSC is known to be very high in the Bay of Plenty. Pathologically reported incomplete excision rates are nevertheless comparable with other studies. Of all skin cancers, those on the head and neck are most commonly associated with incomplete excision. Trained surgeons have significantly higher complete excision rates. | Consultants tended to excise more difficult lesions by anatomical site and by tumour size – possibly leaving wider margins due to their ability to reconstruct the site. | |
| (Williams *et al.* 1991) | To investigate whether GPs submitted more skin lesion biopsy samples for histopathology following the introduction of a new contract in 1990. | Retrospective case series.<br><br>Histopathology department database was interrogated to review skin biopsies sent from primary care over a 1 year period. | 338 skin lesion specimens, from a total of 357 specimens were received from 60 general practices, with 100 GPs.<br><br>**UK** | Proportion of skin specimens that were from histologically malignant lesions in 1989 compared with 1990. | Over the study period 26/233 (11.2%) of the skin specimens were from histologically malignant lesions, as follows:<br><br>BCC (14)<br>SCC (8)<br>Melanoma (4)<br><br>All skin specimens were excision biopsies.<br><br>6 (2.6%) of the skin specimens were from histologically malignant lesions in 1989 compared with 20 (5.9%) in 1990 ($p = 0.024$).<br><br>The authors concluded that the benefits of GPs excising skin cancer tumours early are debated, and that it is essential that GPs who undertake minor surgery are adequately trained and that all biopsy samples are submitted for histological examination. | Small number of skin cancer lesions.<br><br>Study is only able to estimate GP performance based upon samples sent for histological evaluation. | 3 - |

**The question**

*What is the effect of training upon the ability of GPs to correctly diagnose precancerous skin lesions?*

**The nature of the evidence**

**Two randomised controlled studies, of good quality, were identified. Both studies are of primary care physicians in the US, treating patients with lesions suspicious of skin cancer.**

**Summary of the supporting evidence for the recommendations**

**Two RCTs demonstrated that provision of training to GPs significantly improved their diagnostic and management ability with regard to skin lesions, including skin cancer and premalignant lesions. In one study the training was delivered via the internet.**

- The RCT by Gerbert et al. (1998) demonstrated that a brief educational intervention improved the ability of primary care physicians to correctly diagnose melanoma and to plan the optimal management of patients with skin cancer, including melanoma.
- The RCT by Gerbert et al. (2002) found that an internet delivered educational intervention on skin cancer diagnosis and planning was associated with a significant improvement in the ability of GPs in overall diagnosis and evaluation planning, diagnosis of melanoma and seborrhoeic keratosis, diagnosis and evaluation planning of SCC and BCC and evaluation planning for actinic keratosis.

# EVIDENCE TABLE 3.5

## *What is the effect of training upon the ability of GPs to correctly diagnose precancerous skin lesions?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Gerbert *et al.* 1998) | To determine whether a brief, multicomponent educational intervention could improve the skin cancer diagnosis and evaluation planning performance of primary care physicians to a level equivalent to that of dermatologists. | RCT<br><br>Intervention group (n=26): Provided wit educational seminar, diagnostic written material and equipment for clinical examination and feedback on performance.<br><br>Control group (n=26):<br><br>Plus 13 dermatologists. | 52 primary care physicians plus 15 dermatologists.<br><br>**US** | Primary care physicians' ability to diagnose and plan management of patients with skin cancer, pre-test and post-test.<br><br>6 categories of skin lesion were evaluated, including melanoma, SCC and BCC.<br><br>Participants were required to choose from six treatment options, which did not include 'refer to dermatologist'.<br><br>Evaluation was at pre-test, intervention and post-test periods. | All three groups demonstrated improved performance through the study period.<br><br>At post-test, both the intervention and control group demonstrated improved performance, with the intervention group revealing significantly larger gains.<br><br>The intervention group showed greater improvement than the control group across all six diagnostic categories of lesion (a gain of 13 percentage points vs. 5, $p < .05$), including actinic keratosis, seborrhoeic keratosis and naevi, and in evaluation planning for melanoma (a gain of 46 percentage points vs. 36, $p < .05$) and SCC (a gain of 42 percentage points vs. 21, $p < .01$).<br><br>The intervention group performed as well as the dermatologists on five of the six skin cancer diagnosis and evaluation planning scores including actinic keratosis, seborrhoeic keratosis and naevi, with the exception of the diagnosis of BCC.<br><br>The authors concluded that primary care physicians can diagnose and make evaluation plans for cancerous skin lesions, including melanoma, at a level equivalent to that of dermatologists if they receive relevant, targeted education. | Sample and recruitment methods not described.<br><br>There were no significant differences between participants at the start of the study for demographic, dermatology experience and pre-test ability variables.<br><br>Dermatologists did not receive the intervention.<br><br>Some patients with lesions were examined, other lesions (especially melanoma) were examined on slides.<br><br>Of 62 initial participants recruited, 10 primary care physicians retired from the study before the post-test (5 from intervention and 5 from control groups). | 1 ++ |
| (Gerbert *et al.* 2002) | To test whether the educational intervention on skin cancer diagnosis and treatment planning designed by Gerbert et al. (1998) improved the | RCT<br><br>Intervention (n=39): Pre-test, internet tutorial (including | 71 primary care physicians.<br><br>**US** | % of correct answers in pre test and post test, analysed by lesion type for: | From pre-test to post test I, the intervention group showed significantly greater improvement than control group in overall diagnosis and evaluation planning, diagnosis of melanoma and seborrhoeic keratosis, diagnosis and | Only univariate statistical tests used – possible type I errors in numerous (14) outcomes, although some results were significant at $p < 0.01$ or $p < 0.001$. | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | diagnostic and management ability of primary care physicians when used via the internet. | melanoma, SCC, BCC and non malignant lesions), post test I and further post test II 8 weeks later.<br><br>Control (n=32): Pre-test followed by post test I. | | Diagnosis<br><br>Management decision<br><br>Effect of intervention on sample as a whole (non ITT) in subjective confidence (data not shown). | evaluation planning of SCC and BCC and evaluation planning for actinic keratosis.<br><br>In post test II (intervention group only) this advantage was maintained for diagnosis of melanoma, diagnosis and evaluation planning of SCC, overall evaluation planning and evaluation planning for BCC.<br><br>Authors conclude that the internet is an effective medium for training of primary care physicians in the diagnosis and management planning of skin lesions including melanoma, SCC and BCC. | Of 879 initial study accruals only 71 completed the study in full.<br><br>The control group underwent the tutorial after the post test (which should not affect results).<br><br>A greater proportion of the intervention group worked primarily in medical schools.<br><br>In this study, primary care physicians in private practice were under represented. | |

# The role of General Practitioners with a Special Interest in Dermatology

**In addition to the research questions and evidence identified on the role of GPs in the diagnosis and treatment of skin cancer set out above, the British Association of Dermatologists has shown support for the training of GPSIs by consultant dermatologists in diagnostic skills for benign and malignant skin tumours. The British Association of Dermatologists is supportive of clinical governance arrangements for issues such as training, continuing medical education (CME), professional development and accountability, which apply to GPSIs. The British Association of Dermatologists recommends that:**

- **Consultant supervised training sessions for GPSIs is provided, at times set aside from normal clinics**
- **GPSIs are passed as competent by a consultant dermatologist**
- **Arrangements are made for audit of performance**
- **Close links are maintained with dermatology and histopathology specialist departments, possibly through computer links and using telemedicine if appropriate.**

# EVIDENCE TABLE 3.6

## The role of General Practitioners with a Special Interest in Dermatology

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Lawrence 2003) | To summarise the British Association of Dermatologists' (BAD) view on how GPSI services should be organised and training and supervision implemented. | Consensus statement, drawing on Department of Health Guidelines for GPSIs. | GPSIs in dermatology. | | Author reports:<br><br>Dermatologists support the GPSI scheme provided it is adequately resourced and that high quality standards are maintained, through clinical governance arrangements for training, continuing medical education (CME), professional development and accountability.<br><br>GPSIs should have 15 minutes with each patient.<br><br>To fulfil all functions, it is estimated that 100 consultant supervised *training* sessions per GPSI are necessary, aside *service provision* time.<br><br>GPSIs performing skin surgery should be passed as competent by a consultant dermatologist and should demonstrate diagnostic skills with regard to benign and malignant skin tumours, with an understanding of histopathology.<br><br>The GPSI scheme should take account of audit requirements and also of the likely impact on service capacity and of cost. Author concludes that the scheme is yet to be shown as cost effective compared to traditional service. | | 4 |
| (British Association of Dermatologists 2002) | To set out Service Provision Guidelines for General Practitioners with a Special Interest in | Position statement written by expert dermatologists. | General Practitioners with a Special Interest in Dermatology. | Recommendations for practice. | Skin surgery sessions may be undertaken in the community by trained general practitioners with suitable facilities. Appropriate documentation of | Internet based resource. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | Dermatology. | | **UK** | | lesions, including photographic records is essential. Close links to the local dermatology and histopathology departments are essential.<br><br>Those performing skin surgery clinics should have been trained and assessed by a local dermatological surgeon until they are deemed competent. They should gain and demonstrate diagnostic skills on benign and malignant skin tumours. They should understand the necessary histopathological techniques required for diagnosis.<br><br>Any GP performing skin surgery should be an integral part of the local skin cancer service and join the multidisciplinary conferences required in that process. CME, audit and revalidation criteria (described elsewhere in document) should be in place.<br><br>Those undertaking specialized skin surgical work which involves patients with skin cancer should form a part of the local cancer service plan and have appropriate links to histopathology services as well as the specialist dermatologist.<br><br>A computer link to the hospital-based dermatology department is highly desirable with telemedicine facilities if appropriate. | | |

# Multidisciplinary teams

### The question

*Are better outcomes achieved for patients with skin cancer through organisation of care by multidisciplinary care, compared to traditionally organised care?*

### The nature of the evidence

Thirteen studies were identified, as follows:

- One systematic review of poor quality
- Three observational studies, one of fair quality and two of good quality
- Three clinical guidelines of good quality
- Six expert reviews or reports, three of good quality and three of fair quality

Five studies originate from the US, one study is a US / European collaboration, one study is from Australia and five studies are from the UK. Applicability to the UK is therefore limited.

Eight studies address patients treated for skin cancer. Two studies are of groups of patients with different types of cancer. Two studies are of transplant patients.

### Summary of the supporting evidence for the recommendations

**Although the grade of evidence available for multidisciplinary care of patients with skin cancer is generally poor, observational and expert review studies are supportive of this approach, including patients with melanoma. These studies cite benefits for patients and healthcare systems arising from multidisciplinary care, including higher quality of care, cost effectiveness, improved communication between professionals, adherence to guidelines and improved research opportunities. Other studies are supportive of a multidisciplinary approach in specialist settings, i.e. patients with skin cancer following organ transplantation and patients with cancer receiving palliative care.**

**Clinical guidelines produced by expert bodies in the UK support multidisciplinary care as the model of care for patients with melanoma and for patients with high risk**

**SCC. UK guidelines for plastic surgery services strongly support multidisciplinary management of patients with skin lesions and recommend appropriate training and accreditation for all clinicians who perform skin surgery.**

**Audit evidence from the UK suggests that there can be difficulty in setting up effective skin cancer MDTs, which meet the standards that are set out in the Manual of Cancer Services Standards.**

- The expert opinion paper by Chang (1998) is supportive of multidisciplinary teams in the care of patients with melanoma, stating that their use enhances quality of care, impacting on patients' quality of life.

- The observational study by Fader et al. (1998) concluded that treating patients in a multi disciplinary melanoma clinic is cost effective compared to treating patients in the local community, with a saving of approximately $1600 per patient.

- The expert report by Johnson et al. (2000) concluded that the multidisciplinary melanoma clinic model resulted in benefits, including increased staff enthusiasm, coordinated access and communication via nurse coordinators, increased cost effectiveness and efficiency, comprehensive care and research opportunities.

- The retrospective review by McGinnis et al. (2002) found that histological review of excised pigmented lesions by experienced pathologists within the multidisciplinary team provided internally consistent diagnoses and valuable second opinions, including changes in diagnoses from malignant to benign or benign to malignant.

- The expert review by Parry et al. (1999) reported the benefits of a multidisciplinary approach in the treatment of patients with cancer to be: user friendliness, clinical efficiency, cost efficiency; access to novel therapies, quality assurance, education, clinical research and translational research.

- The expert report of a specialist centre to treat patients with melanoma by Thompson et al. (2003) states that the multidisciplinary approach fosters cohesion amongst professionals, encourages adherence to evidence based treatment guidelines, commitment to research and the ability to maintain standards for technically demanding procedures.

- Evidence from the systematic review by Hearn and Higginson (1998) is supportive of a multidisciplinary approach to the palliative care of patients with skin cancer. This study suggests that specialist teams in palliative care improve patient satisfaction and identify and deal with more patient and family needs than conventional care. It also describes that the MDT approach to palliative care reduces the overall cost of care by reducing the amount of time patients spend in acute hospital settings.

- A survey of transplant physicians by Christenson et al. (2004) found that multidisciplinary specialist clinics for dermatological management of transplant patients are highly effective.

- The expert review by Berg and Otley (2002) stated the need for a multidisciplinary approach to therapeutically manage transplant patients with skin cancer, which requires input from surgical, transplant, oncology and radiological groups.

- Clinical guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists recommend that multidisciplinary care is the most desirable model of care for patients with melanoma.

- Clinical guidelines for the treatment of patients with SCC produced by Motley et al. (2003) on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons recommend that patients with high risk, advanced stage or non resectable SCC should ideally be reviewed by a multi-professional oncology team.

- An audit of skin cancer MDT activity in 21 NHS Trusts in England undertaken by Poirier et al. (2004) identified difficulty in setting up effective MDTs, meeting attendance standards and concluded that ideal MDT based care would require significant prioritisation and funding in order to be realised.

- Service guidance produced by the British Association of Plastic Surgeons and NHS Modernisation Agency (2005) is strongly supportive of multidisciplinary management of patients with skin lesions, reporting that up to 25% of Plastic, Reconstructive and Aesthetic surgery referrals relate to minor skin lesions and that the roles of the Plastic, Reconstructive and Aesthetic Surgeon and Dermatologist

overlap. The authors recommend that all practitioners performing skin surgery should have appropriate training and accreditation.

# EVIDENCE TABLE 3.7

***Are better outcomes achieved for patients with skin cancer through organisation of care by multidisciplinary care, compared to traditionally organised care?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Berg & Otley 2002) | To describe the epidemiology, clinical presentation and recommended management of skin cancer during post transplantation immunosuppression. | Evidence based Continuing Medical Education resource of the American Academy of Dermatology (144 references). | Transplant patients (populations from numerous countries in cited studies).<br><br>**Undertaken in the US** | Article addresses epidemiology, cofactors to accelerated carcinogenesis, preventive education and treatment of skin cancer. | SCC is the most common post transplantation malignancy in Caucasian populations and manifests with younger age at onset, higher incidence of multiple tumours and increased aggressiveness. Incidence of skin cancer increases with time since transplant and lower latitude, with increase in incidence as follows:<br><br>SCC: 65 fold<br>SCC of the lip: 20 fold<br>BCC: 10 fold<br>Melanoma: 3.4 fold<br>Kaposi sarcoma: 84 fold<br><br>Overall mortality from melanoma at 5 years is 30% in transplant patients compared with 15% in the general population.<br><br>Skin cancer can be particularly aggressive in child / adolescent patients with higher SCC / melanoma incidence than in adults. Paediatric transplant patients have a skin cancer mortality rate of 8%. Merkel cell carcinoma is also more aggressive in transplant patients than in the general population. A subset of transplant patients develop > 100 SCCs annually.<br><br>Risk factors are older (and paediatric) age, long duration of | Highly evidence based expert review.<br><br>Most data originates from the era of cyclosporine i.e. since 1979.<br><br>Role of immunosuppression is believed to be two fold: i) directly carcinogenic ii) causing reduction in autoimmune surveillance and eradication of precancerous cells.<br><br>The primary pathogenic factor both in transplant patients and the general population is UV light. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | immunosuppression, intense immunosuppression, fair skin, significant prior exposure to UV radiation, HPV infection, lower CD4 count, history of skin cancer prior to transplantation. | | |
| (British Association of Plastic Surgeons & NHS Modernisation Agency 2005) | To provide guidance for patient-centred models of care in the overlap areas between Plastic, Reconstructive and Aesthetic Surgery and Dermatology. | Service Guideline. | Patients with skin conditions for whom Plastic Surgeons have an input to care.<br><br>**UK** | Recommendations for practice. | Guidance provides a model for the care of patients with skin lesions including a recommended patient pathway, supporting joint working between the group's representatives in Plastic, Reconstructive and Aesthetic Surgery and, Dermatology, patient groups and the Skin cancer collaborative.<br><br>**Recommendations**<br><br>**General**<br>1. The diagnostic and management phases of the treatment of skin lesions should ideally be considered separately.<br>2. All practitioners performing skin surgery should have appropriate training and accreditation.<br><br>**Patients**<br>● Supported by coherent Primary and Secondary Healthcare delivery.<br>● Supported in their self-management by access to Skin Lesion diagnostic facilities.<br><br>**Plastic surgeons:**<br>When managing Skin cancer, Plastic Surgeons should be educated in a consistent, nationally agreed, approach to the diagnosis and treatment of Skin Cancers and work to the expectations set by NICE guidance.<br><br>In the management of Skin Cancer in some Health Communities, the roles of the Plastic, Reconstructive and Aesthetic Surgeon and Dermatologist may overlap and require further definition.<br><br>Multi Disciplinary Team working is encouraged as appropriate with clinical colleagues and allied healthcare professionals. | Part of a larger strategy for the planning and delivery of patient-centred Plastic Surgery services within the NHS, titled, *Action On Plastic Surgery (AOPS) Programme.*<br><br>AOPS started in 2002 and has put in place 19 AOPS Pilot Site Projects in England and Wales, (18 funded by the Department of Health (England) and one funded by the Welsh Assembly.<br><br>Associated work has been undertaken in Scotland. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Plastic surgeons should ideally be actively involved in the training and education of their acute sector peers, GPs, members of the Primary Healthcare team and Non Consultant career grade Doctors.<br><br>Plastic surgeons should play an important role in the Skin lesion model for the local health community particularly in relation to diagnosis and management of Skin Cancer.<br><br>Scoping work from AOPS pilot site indicates that up to 25% of Plastic, Reconstructive and Aesthetic surgery referrals relate to minor skin lesions. | | |
| (Chang 1998) | To describe an institution's approach to setting up multidisciplinary clinics for diagnosis and for subsequent follow-up. These are either organ- or disease-specific. | Expert opinion. | Patients with melanoma or lymphoma.<br><br>**US** | | Suggests organisational elements critical to the success of a multidisciplinary clinic:<br><br>Physician-director, nurse co-ordinator, administrator, support staff, members from the clinical disciplines including pathology and radiology, and a tumour board. (the latter to provide timely feedback of information to the patient)<br>Suggests that the multidisciplinary clinic can offer patient education programmes, psychosocial support and rehabilitative services, requiring input from nurses, social workers, physiotherapists and dieticians – all enhancing quality of care and impacting on quality of life. | Author part of a Multidisciplinary Melanoma Clinic – one of the most active in the US (see Johnson paper). | 4 |
| (Christenson *et al.* 2004) | To report on three types of speciality clinics, which are considered to be highly effective for proactive care. | Report based upon qualitative and quantitative survey of 12 physician members of the International Transplant Skin Cancer Collaborative (ITSCC). | Patient population is transplant patients. Survey was of physicians providing care.<br><br>**US / non UK European** | Measures recorded included: patients seen per week, referral scheme, timing of skin examinations, education methods, treatments provided, follow-up schema, research activities and extent (years) of experience. | The three clinic settings were:<br><br>i) Dermatology transplant sub-speciality clinic within a multidisciplinary transplant clinic<br>ii) Designated dermatology clinic for transplant recipients<br>iii) Clinical care of transplant recipients integrated into existing dermatology clinics.<br><br>The authors propose steps to providing the best care, based on this research: | Survey methods not reported. Graded as formal consensus evidence. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | • Close communication between transplant physicians and nurse coordinators;<br>• Education of other care providers about the unique dermatological needs of transplant patients;<br>• Provision of an effective scheduling mechanism for seeing transplant patients in dermatology including baseline / triage assessment;<br>• Education of patients on prevention;<br>• Chemoprophylaxis;<br>• Comprehensive dermatological care;<br>• Close follow-up according to risk and as recommended in ITSCC follow-up guidelines;<br>• Adherence to ITSCC guidelines for management of SCC;<br>• Networking with other dermatologists via ITSCC email services and website. | | |
| (Fader *et al.* 1998) | To evaluate whether co-ordinated multidisciplinary melanoma care that follows evidence-based, consensus-approved clinical practice guidelines at a large academic medical centre can provide a more efficient alternative to traditional community-based strategies with clinical outcomes that are at least equivalent. | Historic cohort for one outcome, case series for others. | Consecutive sample of 104 patients with local disease who were treated in the community compared with 104 blindly selected subjects treated at the multidisciplinary melanoma clinic during an identical time period, matched for Breslow depth and melanoma body site.<br><br>**US** | Cost.<br><br>Surgical morbidity length of hospital stay, (compared with literature) and long-term survival (compared with survival data from the National Cancer Institute) . | Patients treated in the multidisciplinary melanoma clinic would save a third party payer roughly $1600 per patient when compared with a similar group treated in the local community. Surgical morbidity, length of hospitalisation, and long-term survival of multidisciplinary melanoma clinic patients were similar to those reported in the literature. | Authors suggest that the cost discrepancy is explained by the fundamental differences in the usage pattern of healthcare resources exhibited by the multidisciplinary melanoma clinic compared with the community setting. | 3 |
| (Hearn & Higginson 1998) | To determine whether teams providing specialist palliative care improve the health outcomes of patients with advanced cancer and their families or carers | Systematic review of RCTs, comparative and observational studies (18 relevant studies identified) | Any patient with advanced cancer and their families. Specific cancers not described. Information about age and gender not | Aspects of symptom control.<br><br>Patient and carer satisfaction.<br><br>Healthcare | Four out of five RCTs and the majority of comparative studies indicated that the specialist, co-ordinated approach resulted in similar or improved outcomes.<br>Results support use of specialist Multidisciplinary teams in primary care | Some studies from US – different healthcare system.<br><br>Comprehensive search strategy. Hand-searching. Attempts to find unpublished material. All languages | 1- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | when compared with conventional services. | Inclusion criteria: Studies which considered the use of specialist multi-professional teams (MPT) caring for advanced cancer patients and their families. Excluded studies which focused on one cancer site to avoid problems with generalisability Results not combined. | available for all studies .<br><br>Intervention: Diagnosis, treatment, management by multidisciplinary teams.<br><br>**UK** | utilisation and cost.<br><br>Place of death.<br><br>Psychosocial indices.<br><br>Quality of life. | to improve satisfaction of patients with advanced cancer and their family. Evidence suggests Multidisciplinary teams were more able to identify and deal with patient/family needs, and provided access to other services. Teams involving a nurse specialist, GP and a district nurse provided the best services for those patients requiring symptom relief.<br><br>Some studies reported cost information. Results showed a tendency for reduced or equal costs in the intervention group, with reduction in number of inpatient hospital days. Formal analysis not conducted. | considered.<br><br>Validity of primary studies evaluated with grading system. Appropriateness of various outcome measures considered when allocating grade. However, how this was implemented not discussed and results and conclusions did not take them into account.<br><br>Conclusions may overstep the quality of the data in the included studies. | |
| (Johnson *et al.* 2000) | To discuss the organisation of a single multidisciplinary melanoma clinic in Michigan, and how it manages patients. | Expert report of experience of a single centre. | Patients with malignant melanoma treated at a specialist centre.<br><br>**US** | Author's account of experience. | Author reports the benefits of the University of Michigan multidisciplinary melanoma clinic model as increased staff enthusiasm, coordinated access and communication via nurse coordinators, increased cost and efficiency, comprehensive care [particularly with regard to sentinel lymph node biopsy (SLNB) and histopathology] and research opportunities. | | 4 + |
| (McGinnis *et al.* 2002) | To determine whether a pathology review within a multidisciplinary pigmented lesion clinic results in changes in original histological diagnosis and patient management. | Retrospective review of pathology reports at a single centre (case series). 5136 lesions analysed. | Patients with benign or malignant pigmented lesions referred to a specialist centre.<br><br>**US** | Study records % of changes in diagnoses and management decisions. | Pathology review of primary melanocytic lesions within the multidisciplinary pigmented lesion clinic led to revision of original diagnosis in 11% of lesions, with 2.3% revised from malignant to benign or benign to malignant. Review of re-excisions led to a change in margin status in 12% of cases. Biologic behaviour supported changes in histologic diagnosis. Author concludes that review by experienced pathologists within MDTs provides internally consistent diagnoses and valuable second opinions. | Appraised as diagnostic study. Author notes limitations of study owing to prior treatment before MDT review, delays in referral and differential follow-up. | 3 + |
| (Motley *et al.* 2003) | To provide evidence based guidelines on the treatment of patients with SCC on behalf of the British Association of Dermatologists and the British Association of | Clinical guidelines. | Patients with SCC.<br><br>**UK** | Recommendations for clinical practice. | Recommends:<br><br>Patients with high risk SCC and those presenting with clinically involved lymph nodes should ideally be reviewed by a multi-professional oncology team which includes a dermatologist, pathologist, | 82 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | Plastic Surgeons. | | | | appropriately trained surgeon (usually a plastic or maxillofacial surgeon), clinical oncologist and a clinical nurse specialist in skin cancer. Some advanced tumours are not surgically resectable and these should be managed in a multi-professional setting in order that other therapeutic options are considered. | | |
| (Parry *et al.* 1999) | To report on the multidisciplinary approach to treating cancers. | Expert review. | Patients with cancer.<br><br>**UK** | Putative advantages from primary studies. | Discusses the evidence supporting a multidisciplinary approach for the management of patients with cancer, citing papers relating to other cancer sites (breast, ovarian, haematological), and papers relating to the centralisation of services for rare cancers (but some of these are not research studies as claimed, but opinion papers).<br><br>Continues to discuss the specific challenges for the multidisciplinary care of patients with cutaneous lymphomas and describes the multidisciplinary cutaneous lymphoma programme at a hospital in Cleveland Ohio. Refers to benefits of a multidisciplinary approach, including user friendliness, efficiency and cost savings; access to novel therapies, quality assurance, education, clinical research and translational research (none of this section directing referenced in support).<br>Suggests directions for future outcomes-based research involving multidisciplinary programmes. | | 4 |
| (Poirier *et al.* 2004) | To gain a baseline of skin cancer MDT activity in the South West Region, and to compare this against the Manual of Cancer Standards.<br><br>To share best practice across the region. | Audit of activity against local standard, using questionnaire based on the local standard. Data were obtained between December 2003 and February 2004. | 21 NHS Trusts in England – representing patients with skin cancer.<br><br>**UK** | Adherence to standard. | **Summary points:**<br>• 21 responses were received. Response rate reported as 'very good'.<br>• The main area of concern identified was the first step of establishing an effective MDT: only 11/20 units claimed to have an MDT.<br>• No Trust met all of the Cancer Services Standards set out in the questionnaire.<br>• The best attendance to an MDT meeting was achieved with 6 core members attending on a fortnightly basis.<br>• A number of respondents are | | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | currently working towards developing MDTs within their Trust.<br>• The authors conclude that the audit highlights the uniqueness of skin cancer services since generic standards are not always applicable.<br>• An ideal MDT for skin cancer is proposed but is unlikely to be realised until significant priority and funding is made to MDTs and to data collection in skin cancer. | | |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma on behalf of the British Association of Dermatologists. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | **Recommends:**<br><br>Multidisciplinary care is held to be the most desirable model of care for patients with melanoma. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Thompson *et al.* 2003) | To describe the history and functioning of a single, multidisciplinary melanoma unit. | Expert report of experience of a single centre. | Patients with malignant melanoma treated at a specialist centre.<br><br>**Australia** | Author's account of experience. | Author reports that the multidisciplinary centre fosters a strong spirit of unity and cohesion amongst professionals, encourages adherence to evidence based treatment guidelines and is committed to research. Author reports that high volume specialist centres are able to maintain standards for technically demanding procedures e.g. sentinel lymph node biopsy (SLNB), regional lymph node dissections. | | 4 + |

# The role of nurses in the diagnosis of skin cancer

### The question

*How effective are practice nurses in diagnosing skin cancer, compared with other health professionals?*

### The nature of the evidence

Seven studies were identified as follows:

- Four observational studies of fair quality
- One non-randomised, intervention study of fair quality
- One service guideline of good quality
- One expert review of fair quality.

Three studies are from the UK, including the service guideline. One study is from Australia and three studies are from the US. Generalisability to the UK is therefore limited.

Four studies relate to the ability of nurses to recognise skin cancer, in various settings. One study provides comparison of nurses and GPs with dermatologists and one study is of the views of primary care physicians regarding diagnosis by non-physicians. The service guideline is part of a larger programme to develop plastic surgery services in the NHS.

### Summary of the supporting evidence for the recommendations

**Expert opinion evidence suggests that competent dermatology nurses can undertake skin biopsies. Observational study evidence is suggestive of a role for nurses in recognising and referring patients with suspicious lesions to specialists. The same level of evidence has found the sensitivity and specificity of nurses with regard to detecting premalignant and malignant lesions to be variable, whilst training of nurses has been found to be useful in the recognition of atypical mole syndrome. Nurses perform screening to some extent in the US, where the majority of physicians in a large survey were happy with the idea of screening by non physicians. UK Guidelines for plastic surgery services are supportive of the role of specialist nurses in plastic surgery and dermatology be widened, with adequate funding.**

- Service Guidelines produced by the British Association of Plastic Surgeons and NHS Modernisation Agency (2005) recommend that further nurse specialist roles should be created and supported by adequate funding.

- The expert report by Godsell (1998) states, that skin biopsies performed by competent dermatology nurses are beneficial, and also proposes guidelines for practice.

- The double-blind observational study by Katris, Donovan, and Gray (1998) found that nurses in a community skin cancer screening clinic noted 95% of the lesions identified by plastic surgeons as suspicious with a false positive rate of 16%. The authors recommended a role for nurses in referring suspicious lesions to a specialist rather than making true diagnoses.

- The observational study by Maguire-Eisen and Frost (1994) found that the recognition rate of melanoma by oncology nurses, dermatology nurses and nurse practitioners had range 54-68% and that recognition scores for premalignant and benign lesions were lower than this range.

- The non randomised intervention study by Newton Bishop et al. (2000) found that after a brief period of training, previously unskilled GPs and nurses were able to correctly recognise atypical mole syndrome, with a rate of agreement with dermatologists of 94%.

- The large survey of physicians' attitudes by Oliveria et al. (2002) found that 29% of physicians reported a nurse performing skin cancer screening, and 73-79% of family physicians and 60-70% of internists were amenable to having a non-physician perform this role.

- The small, pilot study by Oliveria et al. (2001) found that trained nurse practitioners were able to distinguish between benign and malignant lesions on colour slides with sensitivity 100% and specificity range53% -100%. Sensitivity based upon the decision to refer patients following total body examination had range 67% - 100% and specificity had range 62% - 100%. The sensitivity the ability to correctly identify patients with lesions suspicious of skin had range 50% - 100% and specificity had range 99% - 100%.

# EVIDENCE TABLE 3.8

## *How effective are practice nurses in diagnosing skin cancer, compared with other health professionals?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (British Association of Plastic Surgeons & NHS Modernisation Agency 2005) | To provide guidance for patient-centred models of care in the overlap areas between Plastic, Reconstructive and Aesthetic Surgery and Dermatology. | Service Guideline. | Patients with skin conditions for whom Plastic Surgeons have an input to care.<br><br>**UK** | Recommendations for practice. | **Recommendations for nurses:**<br><br>(i.e. Practice Nurses, School Nurses, Nurse specialists in Dermatology and Plastic ,Reconstructive and Aesthetic Surgery Nurses):<br><br>Nurses should be educated in prevention / health education / support / awareness roles.<br><br>Further nurse specialist roles should be created and supported by funding—the necessary resources required to support these are currently being outlined within the NICE Skin Cancer Guidance. | Part of a larger strategy for the planning and delivery of patient-centred Plastic Surgery services within the NHS, titled, *Action On Plastic Surgery (AOPS) Programme.*<br><br>AOPS started in 2002 and has put in place 19 AOPS Pilot Site Projects in England and Wales, (18 funded by the Department of Health (England) and one funded by the Welsh Assembly.<br><br>Associated work has been undertaken in Scotland. | 4 ++ |
| (Godsell 1998) | To describe the experience of a single centre where the dermatology nurse performed skin biopsies, including local guidelines for practice. | Expert report of experience. | Patients attending a tumour clinic with need for skin biopsy identified by Consultant Dermatologist.<br><br>**UK** | Outcome is reported experience. | Author reports benefits to patients and staff through nurse performed skin biopsies. | Includes local protocol for prerequisite experience and competency and also local clinical guidelines for practice. Exact diagnoses not reported. | 4 |
| (Katris *et al.* 1998) | To determine ability of nurses to detect suspicious skin lesions at a community-based skin cancer screening clinic. | Double-blind observation study. Nurses performance compared with plastic surgeons (taken as gold standard). | Measurement were recorded for 256 patients screened by 2 nurses and plastic surgeons.<br><br>**Australia** | Ability to recognise a suspicious skin lesion compared with a plastic surgeon. | Nurse observations noted 95% of the lesions identified by plastic surgeons as suspicious. False positives were 16%. | Study keen to stress that the role of the nurse is not to diagnose, but to not miss lesions that require further specialist interventions. | 3 |
| (Maguire-Eisen & Frost 1994) | To evaluate nurses' frequency of skin cancer assessment, ability to | Observational study. | 178 nurses, nurse practitioners, oncology nurses, | Tool used captured information about impact of | Participants indicated that skin cancer assessment was within their scope of practice but reported frequencies of | Sample of nurses came from those attending continuing education programmes and | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | recognise melanoma, knowledge of risk factors and preventive measures, teaching practices, and barriers to skin cancer assessment. | | dermatology nurses.<br><br>**US** | specialisation and experience of skin assessment practices; ability to differentiate between benign, premalignant and melanoma lesions (colour slides); knowledge and frequency of teaching risk factors and preventative measures; self-reported barriers. | performance were low. Nurse practitioners scored lower in overall knowledge, although they had received the highest level of formal skin cancer education ($p < 0.05$). Recognition of melanoma was moderate, with scores of 54-68% for the three groups. Recognition scores for premalignant and benign lesions were lower. Frequency of skin cancer assessment and teaching were higher for dermatology nurses ($p < 0.05$). Total knowledge scores were not predictive of teaching practices. Time limitations and inadequate knowledge were barriers that inversely correlated with frequency of skin cancer assessment. | therefore may represent a higher level of education and training than the average nurse. | |
| (Newton Bishop *et al.* 2000) | To determine ability of previously unskilled GPs/nurses to recognise AMS phenotype after brief training. | GPs/nurses trained in use of the AMS scoring system. Performance in diagnosis of AMS compared with that of dermatologists. | 18 GPs/nurses from 5 countries<br>(6 nurses and 0 GPs from UK).<br><br>**UK** | Ability to recognise AMS compared with dermatologists. | Overall agreement in diagnosis between trained non-specialists and dermatologists was 94.5% (kappa 0.7, $p < 0.0001$). | Accurate diagnosis of AMS is possible by trained non-specialists. | 3 |
| (Oliveria *et al.* 2002) | To determine physician use and amenability to use of non-physician healthcare providers to perform skin cancer screening in comparison with other cancer screening examinations. | Attitudinal survey/ survey of current practice. | 1,363 primary care physicians.<br><br>**US** | Numbers of physicians utilising non-physician healthcare providers to perform skin cancer screening and numbers amenable to practice. | 29% physicians reported a nurse performing skin cancer screening. 73-79% of family physicians and 60-70% of internists were amenable to having a non-physician performing this role. | No investigation of accuracy of role. | 3 |
| (Oliveria *et al.* 2001) | To evaluate the ability of trained nurse practitioners to accurately identify suspicious lesions in a clinical setting. | Assessment of nurses ability to detect suspicious lesions following a training programme. | 5 nurse practitioners, working at a Diagnostic and Wellness Centre of a cancer centre hospital. No previous experience in evaluating skin lesions. Training received at accredited nursing programmes.<br><br>**US** | 3 assessments: ability to distinguish between benign and malignant lesions from colour slides (gold standard biopsy-proven); ability to correctly refer patients with suspicious lesions from a population (25) receiving whole body examination (gold | 1st assessment: Sensitivity of all 5 nurse practitioners was 100%, specificity ranged from 53% to 100%. 2nd assessment: referral sensitivity and specificity ranged from 67% to 100% and 62% to 100%, respectively. 3rd assessment: sensitivity for detecting significant skin cancer lesions ranged from 50% to 100% and the detection specificity was 99% to 100%. Preliminary results from a pilot study suggest that nurse practitioners can be trained to accurately identify and triage suspicious lesions. | Convenience sample of small numbers. Self-selected patients.<br>1 nurse had different training from the rest.<br>Equivalence of "nurse practitioners" to UK nurses? | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | standard : dermatologist's assessment); ability to correctly identify patients with suspicious lesions from a population (30) containing 8 with lesions highly suspicious/ characteristic of non melanoma and melanoma (gold standard consensus clinical diagnosis of 2 dermatologists). | | | |

# The impact of delay in diagnosis of skin cancer

### The questions

*Does delay in the referral of patients with lesions suspicious of skin cancer by GPs affect stage of disease at presentation?*

*Does delay in the referral of patients with lesions suspicious of skin cancer by GPs affect survival?*

*Does a delay in presentation of a suspected skin cancer by patients affect stage of disease at presentation?*

*Does a delay in presentation of a suspected skin cancer by patients affect survival?*

### The nature of the evidence

Sixteen studies were identified, as follows:

- Two observational study of good quality
- Thirteen observational studies of fair quality
- One observational study of poor quality

None of the studies identified measured the impact of delay in diagnosis upon survival.

Fourteen studies are of patients with melanoma, where three studies are of the same case series of patients (i.e. those by Richard et al.). One study is of all patients who attended a pigmented lesion clinic over a study period. One study is of patients diagnosed with different types of skin cancer.

Three studies are from the UK. Two studies are from the US, one is from the Republic of South Africa and ten studies are from Western European countries. Applicability to the UK is therefore low.

### Summary of the supporting evidence for the recommendations

**There is no consensus between the observational studies identified, on the relationship between length of delay to diagnosis of melanoma and tumour thickness at diagnosis. Two studies found a positive association between these**

**variables, one study a negative association and two studies no association. Estimates of delays in patients receiving diagnosis of, and treatment for, melanoma vary widely and delay is often broken down into patient and physician components. The largest study identified, which originates from the UK, provides an estimate of delay in diagnosis of melanoma due to physicians with range 5 - 41 months. Eight studies report a total delay in diagnosis of not more than 12 months. Six studies report a patient delay of ten months or less and four studies report a physician delay of four months or less. There is evidence from a French study that patients who are initially seen by dermatologists experience shorter delays and lower tumour thickness than patients who are initially seen by GPs. Survey evidence from the UK suggests that patients perceive delay in the diagnosis of skin cancer to arise from the failure of GPs to recognise the seriousness of their skin conditions.**

**Studies suggest that women, family members and dermatologists are likely to detect melanomas earlier and that patients that are older, male, less educated, living out of towns, and with low awareness tend to have lower rates of self-detection, longer delays before seeking medical advice and greater tumour thickness at presentation. However one study found no gender difference in duration of delay in seeking medical advice.**

**Observational studies report that changes in skin lesions that are recognised by patients found to have melanoma are change in colour, increase in size, increase in elevation and bleeding.**

**The observational studies identified are inconsistent in their findings on the relationship between delay in diagnosis and the prognostic factors of melanoma tumours at presentation.**

- The case series study by Betti et al. (2003) found a significant positive correlation between thickness and size of melanoma tumours with delay in diagnosis, where the majority of delay was attributed to patients.

- The case series study of patients with melanoma by Blum et al. (1999) found that women were more likely to self detect melanoma than men. The mean delay in diagnosis was 8 months, where misdiagnosis by the first physician visited was reported by 18% of all patients to account for the delay in diagnosis. No association was detected between delay in diagnosis and age, gender or tumour thickness.

- The case series study by Brochez et al. (2001b) found the mean delay in diagnosis to be 10 months, with the 2 main components of delay being patient delay (6 months) and physician delay (4 months). Initial misdiagnosis was a suggested cause of physician delay.

- The case series study by Carli et al. (2003) found that detection of melanoma by dermatologists was associated with early diagnosis.

- The case series study by Cassileth et al. (1988) found the mean time to diagnosis to be 12 months, with main components of delay being patient (6 months) and physician (4 months).

- The large, case series study of patients seen at a clinic (which focussed on pigmented lesions) in the UK by Duff et al. (2001) found that less than 2% of patients with melanoma were considered to have experienced delay in diagnosis. The length of delay had range 5 - 41 months and the clinic was found to have sensitivity 98.5%, specificity 89.2% and negative predictive value = 99.9%.

- The case series study by Dunkley and Morris (1991) found the time to diagnosis of melanoma to have range 0-12 months, with the main components of delay being patient (0-2 months) and physician (0-5 months). Physician delay was found to result from mistaken diagnosis.

- The case series study by Krige et al. (1991) found the mean time to diagnosis of melanoma to be 11 months, with main components of delay being patient (10 months) and physician (1 months). No correlation was found between delay in diagnosis and thickness of melanoma tumours.

- The case series study by Montella et al. (2002) found that 60% of patients diagnosed with melanoma waited for 3 months or more from the onset of symptoms to seeking medical attention. 31% of patients waited for 3 months or more between medical consultation and referral for hospital admission. 35% of patients waited for 6 months or more from initial symptoms to surgical treatment. Thicker tumours were associated with non-dermatologist diagnosis.

- The case series study by O'Donnell et al. (1998) found no difference between men and women diagnosed with melanoma, in duration of delay in seeking medical

advice. A delay in seeking healthcare attributable to the patient of 6 months or more delay was found in 53% of patients.

- The case series study by Oliveria et al. (1999) found the delay attributable to patients diagnosed with melanoma in seeking medical help had mean 2 months (range 0.5-22 months).

- The case series study by Richard et al. (1999) found that patients with self-detected melanoma averaged 21 months (range 0-57 months) between first noticing the lesion and receiving treatment. A negative correlation was found between melanoma tumour thickness and delay to seeking medical advice.

- The case series study by Richard et al. (2000a) found that the thickness of melanoma tumours tended to be lower in cases where patients initially detected the lesion. The median patient delay before recognising lesion of concern was 4 months, to seeking medical advice 2 months, and to treatment 1 week.

- The case series study by Richard et al. (2000b) found that melanoma tumour thickness was lower in physician detected tumours than patient detected tumours. Patients experienced shorter medical delays and had thinner tumours where they initially saw dermatologists, compared to patients who initially saw GPs.

- The case series study by Schmid-Wendtner et al. (2002) found that 55% of patients diagnosed with melanoma waited for 3 months or more from symptom onset to seeking medical attention (i.e. patient delay). 14% of patients waited for 3 months or more between medical consultation and treatment.

- The survey undertaken by the Skin Cancer Guideline Development Group on behalf of NICE (2004) found that one third of the patients responding had experienced delays in diagnosis of skin cancer. Many of these delays were attributed by patients to failure on behalf of GPs to recognise the seriousness of the condition.

# EVIDENCE TABLE 3.9

***Does delay in the referral of patients with lesions suspicious of skin cancer by GPs affect stage of disease at presentation?***

***Does delay in the referral of patients with lesions suspicious of skin cancer by GPs affect survival?***

***Does a delay in presentation of a suspected skin cancer by patients affect stage of disease at presentation?***

***Does a delay in presentation of a suspected skin cancer by patients affect survival?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Betti *et al.* 2003) | To investigate the factors related to early detection of melanoma and assess the possible correlations and effects of these factors upon delay. | Case series. | 216 patients aged 16 to 92 years with melanoma attending dermatology clinic.<br><br>**Italy** | Mode of discovery, delay in diagnosis, thickness and size. | Family members detected lesions in men more frequently, while in women self-detection was more common. The mean delay in diagnosis was 8 months, with the major component of delay being the patient's lack of concern (6 months). Significant positive correlation between thickness and size of tumour with delay in diagnosis. | Time to diagnosis was not influenced by visibility of the tumour, or socioeconomic status. There was a suggestion of a shorter delay in diagnosis arising in patients who were not single.<br><br>Validity of questionnaire was not reported. | 3 |
| (Blum *et al.* 1999) | To identify factors associated with the detection of cutaneous melanomas and reasons for delay in diagnosis and treatment. | Case series. | 429 patients with histologically proven melanoma that were operated on.<br><br>**Germany** | Modality of discovery, clinical symptoms of melanoma, time to diagnosis, proportion misdiagnosed. | Melanoma was more often self-detected by women than men. Patients who self-detected had a longer delay to treatment. The three predominant clinical symptoms recognised by patients were change in colour (darker), increase in size, and increase in elevation. The mean delay in diagnosis was 8 months. A misdiagnosis by the first physician visited was reported by 18% of all patients to account for delay in diagnosis. | No association between delay in diagnosis with (a) age, (b) gender and (c) tumour thickness. | 3 |
| (Brochez *et al.* 2001a) | To examine the diagnostic pathway for patients with cutaneous melanoma in order to | Case series. | 130 patients aged 18 to 89 years from a melanoma registry in the province of | Time to diagnosis, clinical symptoms of melanoma. | The mean delay in diagnosis was 10 months, with 2 main components of delay (a) patient delay (6 months) and (b) physician delay (4 months). | Patient delay was not influenced by age, gender or socioeconomic status. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | quantify both patient and physician delay, and to define factors related to it. | | East Flanders.<br><br>**Belgium** | | The three main clinical symptoms recognised by patients were colour change, increase in size, and elevation. | Physician delay most likely involves (initial) misdiagnosis. Underestimation of physician delay as 40% of questionnaires completed by treating physician. | |
| (Carli *et al.* 2003) | To investigate patterns of detection and variables associated with early diagnosis of melanoma in a population of intermediate risk. | Case series of 816 patients with melanoma treated at 11 centres. Patients received a questionnaire and were dermatologically examined. Multi variable analysis performed. | White people in Italy with histologically confirmed melanoma, post initial excision.<br><br>**Italy** | Main outcome measure is relationship between patterns of detection and patient/physician delay. Melanoma thickness is presented as a binary variable. OR for detection of lesion > 1mm thickness is used. | 331 patients (40.6%) self detected melanoma. 12.5% were detected by spouses and 38.7% by physicians. Female sex (OR 0.70 [0.50-0.97]), high educational level (0.44 [0.24-0.79]) and performance of SE (0.65 [0.45-0.93]) were associated with thinner tumours. 48% of patients performed SE, but only 20.4% regularly. When adjusted for these variables, detection by dermatologist was associated with early diagnosis (OR 0.45 [0.28-0.73]. Author concludes: patterns of detection in Mediterranean population is similar to studies of fair skinned people and supports role of SE and recommends total skin examination by dermatologists be performed to identify suspicious lesions. | Patient characteristics described. | 3+ |
| (Cassileth *et al.* 1988) | To describe behavioural and clinical aspects of tumour recognition and control. | Case series. | 275 patients aged 19 to 83 years attending two melanoma clinics in Philadelphia (n=130) and San Francisco (n=145).<br><br>**US** | Time to diagnosis, components of delay, clinical symptoms of melanoma. | The mean time to diagnosis was 12 months, with main components of delay being patient (6 months) and physician (4 months).<br>Time to diagnosis was shorter for lesions with pigmentation.<br>Changes in colour and diameter were most commonly reported symptoms. | No differences were found between the two clinic-based groups in terms of histology or socioeconomic status. | 3 |
| (Duff *et al.* 2001) | To examine the effectiveness of melanoma diagnosis in a pigmented-lesion clinic (PLC). | Case series. | All 9968 patients attending a Bristol PLC between Jan 1st 1993 and 31st Dec 1998.<br><br>**UK** | Total number of melanomas diagnosed, and proportion missed/delayed. Sensitivity and specificity of PLC in diagnosing melanoma. | Approximately 6% (n=586) of patients diagnosed with melanoma. Nine melanomas (<2%) were considered to have been missed or delayed. The delay in diagnosis of the missed melanomas varied from 5 to 41 months.<br>Sensitivity = 98.5%<br>Specificity = 89.2%<br>Negative Predictive Value = 99.9%. | Only ascertained physician delay. | 3+ |
| (Dunkley & Morris 1991) | To identify the reasons for delays in diagnosis of CMM. | Case series. | 199 patients with a histological diagnosis of CMM in the Tayside Region.<br><br>**UK** | Time to diagnosis, components of delay, clinical symptoms of melanoma. | The time to diagnosis ranged from 0-12 months, with main components of delay being patient (0-2 months) and physician (0-5 months).<br>The most commonly reported symptoms resulting in patient seeking consultation were change in size or colour, and | Physician delay result of mistaken diagnosis, most commonly associated with acral lentiginous melanoma. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | bleeding. | | |
| (Krige *et al.* 1991) | To define the extent of delay and the consequences of such delay in a sequential group of patients with newly diagnosed melanoma. | Case series. | 250 patients aged 15 to 87 years with Stage I biopsy confirmed primary CMM.<br><br>**South Africa** | Time to diagnosis, components of delay, clinical symptoms of melanoma, thickness of melanoma. | The mean time to diagnosis was 11 months, with main components of delay being patient (10 months) and physician (1 months).<br>Patient delay greatest for LMM while physician delay greatest for ALM.<br>Changes in colour and diameter were most commonly reported symptoms.<br>No correlation found between delay in diagnosis and thickness of melanoma. | Asymptomatic melanomas incidentally diagnosed during routine skin surveillance were significantly more favourable (mean depth 0.89mm) than symptomatic melanoma (1.76mm, $p < 0.01$). | 3 |
| (Montella *et al.* 2002) | To examine the relationship between tumour thickness with diagnosis / treatment delay and sociodemographic variables. | Case series. | 530 patients receiving surgery for histologically confirmed melanoma at a tertiary care facility.<br><br>**Italy** | Delay in diagnosis, components of delay, clinical symptoms of melanoma, thickness of melanoma. | 60% of patients waited for >3 months from symptom onset to seeking medical attention. 31% of patients waited for >3 months between medical consultation and referral for hospital admission. 35% of patients waited for >6 months from initial symptoms to surgical treatment.<br>The most commonly reported symptoms were change in size and bleeding. | Thicker tumours associated with (a) males, (b) low level of education, (c) unemployment, (d) symptomatic diagnosis, (d) non-dermatologist diagnosis, (e)NM, and (f) patient delay.<br><br>Validity of questionnaire? | 3 |
| (O'Donnell *et al.* 1998) | To examine clinical and histopathological features of melanoma, and identify risk groups. | Case series. | 213 patients with histologically proven primary CMM (stage I) seen at a Dublin hospital.<br><br>**Ireland** | Age at diagnosis, delay in seeking medical advice, site and tumour thickness. | Females presented a decade earlier than males on average (i.e. age presentation in cohort).<br>There was no gender difference in duration of delay in seeking medical advice. 53% sought advice >6 months of noticing a new lesion or change in pre-existing lesion.<br>Majority of lesions were lower limb in women and trunk in men.<br>Males appear to have thinner lesions than female. | All patients reviewed were seen by 1 of 2 dermatologists.<br><br>All histology reported by 1 pathologist with special interest in dermatopathology. | 3 |
| (Oliveria *et al.* 1999) | To examine the relationship between patients knowledge and awareness of melanoma with delay in seeking medical advice and prognostic outcome variables. | Case series. | 225 cases aged >18 years with cutaneous melanoma identified from the Connecticut Tumour Registry that were part of a population based case-control study.<br><br>**US** | Delay in seeking medical attention, tumour thickness. | The mean delay time was 2 months (0.5-22 months).<br>Increased knowledge/awareness was associated with reduced delay time.<br>Awareness of skin changes was associated with reduced Breslow depth for stage I melanomas. | Validity of measures related to melanoma knowledge and awareness.<br>Small number of individuals (n=36) who were classified as delay in seeking medical attention. | 3 |
| (Richard *et al.* 1999). | To assess correlation between delay in diagnosis and Breslow thickness. | Case series. | 590 patients aged >12 years with histological diagnosis of melanoma, and interviewed within 12weeks of | Tumour thickness and 5 successive time intervals for assessing delay: (1) lesion first noticed (2) lesion causing concern | Patients with self-detected melanoma averaged 21months (0-57 months) between lesion first noticed and resection.<br><br>A weak positive correlation between tumour thickness and delay to | No difference in delay components by gender.<br><br>Older people tended to seek medical advice sooner after lesion becomes concern. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | resection, from 18 public hospital dermatology departments.<br><br>**France** | (3) medical advice sought (4) removal of lesion proposed (5) resection performed. | identifying lesions as causing concern.<br><br>A negative correlation between tumour thickness and delay to seeking medical advice.<br><br>No correlation between thickness and physician delays. | Histological confirmation of diagnosis by 2 experts.<br><br>Validity of questionnaire not reported. | |
| (Richard *et al.* 2000a) | To assess the role of patients in delays in diagnosis and melanoma prognosis. | Case series. | 590 patients aged >12 years with histological diagnosis of melanoma, and interviewed within 12weeks of resection, from 18 public hospital dermatology departments.<br><br>**France** | Patient characteristic, tumour thickness and 5 successive time intervals for assessing delay: (1) lesion first noticed (2) lesion causing concern (3) medical advice sought (4) removal of lesion proposed (5) resection performed. | More than 70% of melanomas were self-detected (proportion of females higher). Median tumour thickness lower when lesion first detected by patient. Median delay before recognising lesion of concern 4 months, medical advice sought 2 months, and before resection 1wk.<br>Patients that were older, male, less educated, living out of towns, and with low awareness tended to have (a) lower rates of self-detection, (b) longer delays before seeking medical advice, (c) greater tumour thickness. | Same patient population as above. | 3 |
| (Richard *et al.* 2000b) | To assess the role of doctors in delays in diagnosis and melanoma prognosis. | Case series. | 590 patients aged >12 years with histological diagnosis of melanoma, and interviewed within 12weeks of resection, from 18 public hospital dermatology departments.<br><br>**France** | Tumour thickness and medical components of delay (time points 3, 4, 5 above). | Physicians coincidentally detected 29% of melanomas, and tumour depths were lower than patient detected melanomas. Physician sensitivity from diagnosis was 86%.<br>Mean time to proposal of lesion removal was 3.5 months, while mean time to resection being performed was 2 months.<br>Compared to patients visiting GPs those seen by dermatologists experienced shorter medical delays and lower tumour thickness. | Same patient population as above.<br><br>Location on acral areas and lack of pigmentation was associated with longer medical delays.<br><br>Validity of the measure of the appropriateness of doctor attitude? | 3 |
| (Schmid-Wendtner *et al.* 2002) | To investigate the extent and consequence of patient and professional delay in patients with melanoma. | Case series. | 233 patients aged 20-88 years with primary cutaneous melanoma diagnosed and treated at single centre.<br><br>**Germany** | Delay in diagnosis, components of delay, clinical symptoms of melanoma, thickness of melanoma. | 55% of patients waited for >3 months from symptom onset to seeking medical attention. 14% of patients waited for >3 months between medical consultation and excision.<br>The most commonly reported symptoms were change in colour and increase in size or elevation.<br>Greater tumour thickness was associated with fairer skin types, lower education, and lack of knowledge. | Validity of measures related to melanoma knowledge.<br><br>Validity of questionnaire?<br><br>Potential underestimation of physician delay? | 3 |
| (Skin Cancer Guideline Development Group on behalf of NICE 2004) | To measure the experience of patients with skin cancer in the UK. | Qualitative survey. | 94 patients with skin cancer of different types: melanoma (55), non-melanoma | Patients reported experience of diagnosis, referral, treatment and | **Quantitative results**<br><br>• 30/58 patients reported a delay in being told the diagnosis of skin | Data missing for a proportion of patients for many outcomes, therefore denominators in proportions | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | (24), unclassified (11), missing data (4).<br><br>Age range reported categorically – the majority of patients were aged between 30 and 70 years.<br><br>**UK** | follow-up and their reported associated emotions.<br>Patients' reported need for information and support. | cancer.<br><br>**Qualitative results**<br><br>• One third of the patients responding to the survey had experienced delays in diagnosis. Many of these were attributed by patients to failure on behalf of GPs to recognise the seriousness of the condition and this prompted the wish for better GP education. Reactions to the delay ranged from anger through to concern. | are based upon patients for whom data are available in each case. | |

# The role of histopathology services

### The questions

*What is the accuracy and consistency of histopathological diagnosis of melanoma?*

### The nature of the evidence

Nine observational studies, of fair quality, were identified. Of these, two originate from the UK, one study is from the US, one study is from Australia, two studies are from Holland and one study each is from France and Belgium. One study was collaboratively undertaken in the US and Europe. Applicability to the UK is therefore limited.

Four studies are of the histological diagnosis of melanoma by general pathologists. Three studies are of dermatopathologists, one study is of dermatologists and one study is of histopathologists.

### Summary of the supporting evidence for the recommendations

**Observational studies provide evidence of high histopathological sensitivity and specificity for melanoma, but also report difficulty with diagnostic accuracy and consistency for borderline lesions. Studies vary in their estimates of concordance between pathologists, depending on whether the study performs a primary versus expert review of pathology slides and also the types of lesion studied: borderline lesions inherently produce lower concordance. Concordance between pathologists is potentially high: of 4 studies providing Kappa values for concordance in adult lesions, K values range from 0.53 to 0.88. There is evidence of particular difficulty in reaching agreement for childhood melanoma, with K range 30.8 to 37.7, based upon one retrospective study. Similarly the studies suggest that dysplastic and Spitz naevi present a particular challenge in histopathological diagnosis.**

- The retrospective study by Barnhill et al. (1999) found that a panel of 10 dermatopathologists found no consensus on classification of 30 lesions as Spitz naevi or melanoma. There was little correlation between diagnosis and outcome and the authors concluded that the diagnosis of many Spitz tumours is difficult, even for experts and especially where lesions have atypical features.

- The observational study by Brochez et al. (2002) found the overall sensitivity (based upon reference diagnosis) for detecting melanoma by 20 general pathologists viewing slides, to be 87% (range 55% to 100%). Sensitivity was lower for tumours less than 1 mm in thickness. The overall specificity for melanoma between the pathologists was 94% (range 83% to 100%).

- The prospective study by Clemente et al. (1991) found that a panel of 6 dermatopathologists reached concordance of diagnosis in 92% of 114 pigmented lesions reviewed. Concordance was 95% for benign acquired naevi, 88% for dysplastic naevi and 92% for radial growth phase melanoma. The authors concluded that concordance was generally high and that the greatest disparity occurred in the differentiation of dysplastic naevi with severe atypia from malignant melanoma in situ.

- A retrospective study of melanoma diagnosis by 8 histopathologists using standardized diagnostic criteria was undertaken by Cook et al. (1996). The authors concluded that the use of the criteria improved the consistency in diagnosis of melanoma with the result that 17% of lesions were re-classified by the panel as benign with atypia and 2% of lesions initially reported as benign were judged to be melanoma.

- The observational study by the CRC Melanoma Pathology Panel (1997) found that agreement between a moderately sized sample of pathologists and a smaller specialist panel of pathologists on the diagnosis of melanoma was higher where the same standard diagnostic criteria were used.

- The retrospective study by de Wit et al. (1993) measured the agreement between 10 dermatopathologists on the diagnosis of melanocytic lesions and found that agreement based upon choosing between benign or malignant was high (90%) whereas agreement based upon more precise diagnosis (using 6 categories) was 70%. There was low agreement on the degree of atypia observed (28%).

- The retrospective study by Scolyer et al. (2003) concluded that agreement among a panel of 6 pathologists for measurements of melanoma tumour thickness, ulcerative state, and tumour mitotic rate was high and that agreement for Clark level in primary cutaneous melanomas was fair to good.

- The retrospective study by Veenhuizen et al. (1997) used a panel of 3 pathologists to review 1069 consecutive slides of melanoma. The panel provided unequivocal diagnosis in 93% of cases. Diagnostic difficulties most often encountered with Spitz naevi and dysplastic naevi. Although the rate of over diagnosis and under diagnosis by referring pathologists was quite high, in the majority of cases the diagnosis of the referring pathologist matched that of the panel.

- A retrospective review of histology slides from children with melanoma by 8 expert dermatopathologists was undertaken by Wechsler et al. (2002) with the conclusion that the reliability of diagnosis of melanoma in childhood is poor, even when submitted to experts.

# EVIDENCE TABLE 3.10

## *What is the accuracy and consistency of histopathological diagnosis of melanoma?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Barnhill *et al.* 1999) | To assess inter observer agreement on diagnosis of melanocytic lesions with some features of Spitz naevi and to assess the prognostic power of histological criteria. | Observational study. | Observers: Panel of 10 dermatopathologists.<br><br>Lesions: 30 melanocytic lesions removed from 28 patients. Lesions had to have some criteria for Spitz naevi. Some conventional melanomas were also included.<br><br>Lesions were assessed independently and blinded to clinical data and classified as: typical Spitz naevus/tumour; atypical Spitz naevus/tumour; melanoma; tumour with unknown biological potential; other melanocytic lesion. | Consensus on classification of melanocytic lesions. | 17 of the 30 lesions were classified by most observers as having some features of Spitz naevi/tumour.<br>There was no consensus (defined as agreement between 6 or more pathologists) on classification as typical Spitz naevus/tumour; atypical Spitz naevus/tumour; melanoma; or tumour with unknown biological potential.<br>4 patients had no evidence of disease after 6 to 14 years; 9 patients had local or regional relapse and 4 died of metastases. There was no consensus regarding diagnostic category and little correlation between diagnosis and outcome.<br><br>13 of the 30 (report says 31 in text) lesions were classified by 7 or more pathologists as melanomas with conventional features (9 patients had local recurrence, metastases or died from disease).<br>4 lesions from the Spitz naevus/tumour classification were classified as melanomas by 6 or more pathologists (patients experienced either recurrence/metastases). | The authors concluded that the diagnosis of many Spitz tumours was difficult even for experts and especially for lesions with atypical features. They also concluded there was a lack of objective criteria for distinguishing Spitz tumours from melanomas and for assessing their malignant potential but that there was a biological relationship between Spitz naevus/tumour and melanoma.<br><br>*Small number of lesions from patients that had long term follow-up or bad outcomes so sample may not be typical of this type of lesion.*<br>*No details of training or experience of pathologists so not possible to assess generalisability of results.* | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | **US** | | | | |
| (Brochez *et al.* 2002) | To evaluate the inter-observer variation in diagnosing clinically suspicious pigmented skin lesions under routine practice conditions. | Retrospective Observational study. | Observers: 20 general pathologists (experience:0.5 to 34 years, mean 14 years).<br>Load of pigmented skin lesions within routine practice (4 to 50 per week, mean 16). Pathologists were volunteers, most recruited during training session.<br><br>Lesions: 46 slides of Pigmented skin lesions with clinically suspicious features (asymmetry, border irregularity, colour variegation.<br>Size > 6mm, elevation, increase in size or darkening of a mole. Reference diagnoses were common naevus (32); dysplastic naevus (7); congenital naevus (2); blue naevus (3); Reeds naevus (2).<br><br>Observers classified slides as: melanoma: in situ/invasive/no primary tumour; common naevus/junctional compound/intradermal ; atypical/dysplastic naevus | Agreement between observers diagnosis and reference diagnosis (initial diagnosis made at dermopathological dept in which 80% of pathologist in agreement or diagnosis made by expert panel of 3 dermopathologists)<br><br>Sensitivity, specificity and positive (PPV) and negative predictive value (NPV) for diagnosis of melanoma. | Agreement between observer and reference diagnosis was: for common naevus 75.6%; dysplastic naevus 45.6%; congenital naevus 45.7%; blue naevus 42.6%; Reeds naevus 47.4%.<br><br>The overall sensitivity for melanoma for observers compared with reference diagnosis was 87%, range (55% to 100%).<br>Sensitivity lower for thin (Breslow thickness < 1mm) than for thick melanomas (83% vs. 97% p = 0.005).<br><br>The overall specificity for melanoma between observers was 94%, range 83% to 100%.<br><br>False-positive melanoma diagnosis; dysplastic naevus (46%, with 44% of junction type), blue naevus (30%), common naevus (14% with 11% of junction type), Reed's naevus (4%) and non-melanocytic lesion (7%). | Author concluded there is a tendency to over diagnose especially thin melanomas. Visual interpretation of histological diagnosis is subjective and significant progress could be obtained by new diagnostic techniques especially in borderline cases.<br><br>*No patient details given. Biopsies were said to be randomly selected. Protocol was approved by all participants before start of study, diagnostic criteria was not discussed before start so as to retain as close to normal routine practice as possible.*<br>*Sets of slides were not completed by all pathologists (90% of all expected evaluations). For some diagnostic categories there were very few examples.* | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | junctional/compound; congenital naevus; blue naevus; Spitz naevus; pigmented spindle cell; and other.<br><br>**Belgium** | | | | |
| (Clemente *et al.* 1991) | To assess concordance among pathologists for histopathologic diagnosis of Dysplastic Naevi. | Prospective study. | Observers: 6 dermatopathologists.<br><br>Discussed and agreed diagnostic criteria of a dysplastic naevus.<br><br>Total number of cases: 114.<br><br>Each observer contributed between 20 and 30 cases divided approx equally between benign acquired naevi, dysplastic naevi and early (radial-growth-phase) melanomas.<br><br>No pathologist re-examined cases from own centre.<br><br>Of 114 slides 84 examined by each of 6 observers.<br><br>**Multinational: US / European** | Inter observer agreement for histopathologic diagnosis of dysplastic naevi. | Mean Concordance for diagnosis:<br>Benign acquired naevi (95%)<br>Dysplastic naevi (88%)<br>Radial-growth-phase-melanoma (92%)<br>Overall concordance (92%).<br><br>Concordance with original histopathologic diagnosis was 82%. | Authors concluded that there was 100% concordance in many cases. Disparities were found in some cases due to difficulties in appreciating atypia or failure to adhere to defined criteria. Greatest disparity occurred in differentiation of dysplastic naevi with severe atypia from malignant melanoma in situ.<br><br>***Cases collected sequentially as submitted by centres.***<br>***No patient information given.*** | 3 |
| (Cook *et al.* 1996) | To evaluate consistency in use of histopathological terms for features of diagnostic and prognostic importance for cutaneous | Retrospective study. | Observers:<br>8 histopathologists.<br><br>Circulation 1:<br>30 lesions studied using observers own | Inter observer agreement for diagnostic and prognostic criteria. | Agreement on diagnoses:<br>Benign with or without atypia: K 0.77<br>Melanoma with Breslow <0.76mm: K 0.63.<br>Melanoma with Breslow ≥0.76mm: K 0.84. | Authors concluded that the use of standardized diagnostic criteria with precise definitions has been shown to improve consistency in diagnosis and | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | malignant melanoma. | | personal definitions of criteria before any discussion.<br><br>Series of meetings held to clarify understanding and use of terms, reviewing selected slides.<br><br>Circulations 2 and 3: 95 lesions including 30 original slides plus 65 additional lesions. Subset of 41 of 95 slides on which there had been most disagreement reassessed in Circulations 4 and 5. Slides reviewed independently but information on age of patient and site of lesion available.<br><br>95 lesions; Compound or junctional naevi without atypia (15); Dysplasia (32) Melanomas (either in situ or with Breslow thickness <0.76mm) (22); Melanomas with thickness ≥0.76mm (26).<br><br>Distribution on 41 slides recirculated: Compound or junctional naevi | | Of original diagnosis of melanoma, 17% were re-classified by observers as benign with atypia; 2% reported to be benign were judged to be melanoma. (This reflected the high proportion of borderline lesions in the study). | it is recommended for general application.<br><br>*No patient details given*<br>*Samples selected by stratified random sampling.*<br>*May not be representative of general histological practice.*<br>*Observers did not read same slides – each observer had one set of 95 slides cut from representative block of 95.* | |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | without atypia (1); Dysplasia (6); Melanomas (either in situ or with Breslow thickness <0.76mm) (16); melanomas with thickness ≥0.76mm (18).<br><br>**UK** | | | | |
| (CRC Melanoma Pathology Panel 1997) | To investigate observer variation in the diagnosis of thin cutaneous malignant melanoma and related lesions in a nation- and at a wide sample of histopathologists in the UK.<br><br>NB MIN = melanocytic intra-epidermal neoplasia. | Prospective diagnostic before and after (observational) study.<br><br>Two circulations of slides<br>In the first, nationwide observers used no standardised criteria whereas the CRC Panel did.<br>In the second, observers and Panel used the same standardised criteria (MIN and the vertical growth phase). | Observers:<br>148 pathologists (76% of randomly selected sample)<br>and<br>Cancer Research Campaign (CRC) Melanoma Pathology Panel (seven histopathologists and one dermatopathologist).<br><br>First circulation, nationwide observers used no standardised criteria whereas the CRC Panel did: 20 slides including benign naevi with no atypia(4); benign naevi with atypia(5); borderline benign/melanoma (1); melanoma thickness (5 < 0.76 mm thick and 5 from 0.76 to 2.77 mm thick).<br>Second circulation: 25 slides (16 from first round + 6 new slides) including benign (5); MIN with no micro | Inter observer agreement for diagnosis using Kappa statistic (K). | First circulation (nationwide observers used no standard criteria)<br>Agreement was lower for the nationwide observers than for the CRC Panel (K = 0.45 versus 0.75). Wide variation in diagnoses by nationwide observers.<br><br>Second circulation (nationwide observers using same standard criteria as Panel).<br>Agreement was similar for the nationwide observers and for the CRC Panel (K = 0.63 and 0.64). Agreement was higher (K = 0.68 for both lots of observers) using only three categories (benign, MIN with or without micro invasion and melanoma with vertical growth phase). | Authors concluded that standardised criteria are needed to reduce observer variability in the diagnosis of melanoma. There is a need for MIN to be evaluated in a larger sample.<br><br>The authors stated that the level of agreement was not high either for the nationwide observers of the Panel but point out that the slides were difficult borderline lesions.<br><br>*Sample of nationwide pathologists was randomly selected and response rate was high. So sample likely to be representative.*<br>*Relatively small number of slides with few falling into each diagnostic classification.*<br>*Some slides were read twice and its not clear if this familiarity would increase the diagnostic accuracy on the second circulation.* | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | invasion (6); MIN with micro invasion (4); MIN with micro invasion/ melanoma with vertical growth phase (2); melanoma with vertical growth phase (8).<br><br>**UK** | | | | |
| (De Wit *et al.* 1993) | To assess the inter observer agreement between 10 dermatopathologists on 50 histological slides of cutaneous melanocytic lesions with an emphasis on dysplastic naevi. | Retrospective study. | Observers: 10 dermopathologists individually diagnosed slides containing cutaneous melanocytic lesions.<br><br>Lesions: 50 histological slides: included 9 non-dysplastic benign melanocytic lesions; 25 dysplastic naevi; 7 melanomas *in situ;* and 9 invasive melanomas.<br><br>All lesions were evaluated independently by 10 dermopathologists within a period of three weeks.<br>Classified into 6 categories: benign proliferation of melanocytes, except Spitz naevus and freckle; common naevocellular naevus with minor abnormal features; dysplastic | Inter observer agreement on diagnosis ( benign vs. malignant, all 6 diagnostic categories and degree of atypia), and inter observer agreement on 20 defined histopathological features using the kappa statistic (K).<br><br>Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values for each of the 20 histological features in distinguishing dysplastic naevi from non-dysplastic naevi.<br>Used discriminant analysis to determine features with greatest power to distinguish dysplastic naevi from non-dysplastic | Agreement for benign compared with malignant was high; percentage agreement 90%, K 0.76.<br><br>Agreement for all 6 diagnostic categories was acceptable; mean percentage agreement 70%; K 0.61.<br><br>There was low agreement for degree of atypia; percentage agreement 28%.<br><br>Agreement for dysplastic naevi compared with non-dysplastic naevi was good, percentage agreement 87%.<br><br>The four histological features with greatest power to distinguish dysplastic naevi from non-dysplastic naevi were: irregular nests, lymphohistiocytic infiltrate, marked junctional proliferation and large nuclei.<br>Using all 4 features: sensitivity was 0.53, specificity was 0.93, PPV was 0.95, NPV was 0.45.<br>Using at least 3 features: sensitivity was 0.86, specificity was 0.91, PPV was 0.96, NPP was 0.73. | The authors concluded that it is possible to reliably diagnose dysplastic naevi by histopathological examination.<br><br>*Exploratory study aimed at defining criteria that may be useful in distinguishing dysplastic naevi from non-dysplastic naevi.* | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | naevus; melanoma in situ invasive melanoma; and other diagnoses.<br><br>Observers were provided with definitions of histological feature but no criteria were suggested for distinguishing between dysplastic naevi and non dysplastic naevi.<br><br>**Holland** | naevi. | | | |
| (Scolyer *et al.* 2003) | To assess inter observer reproducibility of major pathologic prognostic parameters in cutaneous melanoma. | Retrospective study. | Observers:6 pathologists of differing experience.<br><br>69 cases (1 slide per case) of primary cutaneous melanoma Results only reported for 64 cases.<br><br>Recorded assessments of Breslow thickness (mm); tumour mitotic rate (per mm2; Clark level, and ulcerative state.<br><br>Observers given definitions for each assessed pathologic variables.<br><br>**Australia** | Inter observer agreement for histopathologic prognostic variables assessed using Kappa statistic (K) . | Intra class correlation coefficients:<br>Breslow Tumour Thickness: 0.96<br>tumour mitotic rate: 0.76.<br><br>Kappa score:<br>Ulceration: K 0.83<br>Clark Level: K 0.60<br>Level II tumours: K 0.53<br>Level III tumours: K 0.53<br>Level IV: K 0.55<br>Level V: K 0.76. | Authors concluded that the study demonstrated excellent agreement among observers for measurements of tumour thickness, ulcerative state, and tumour mitotic rate and fair to good agreement for Clark level in primary cutaneous melanomas. Given significance of tumour mitotic rate in determining patient prognosis it is important that pathologists measure and record this highly reproducible parameter for all primary cutaneous melanoma.<br><br>*Study states observers blinded but not clear to what degree.*<br>*No patient details given or how many slides in each category.* | 3 |
| (Veenhuizen *et al.* | To identify the most | Retrospective | Observers: 3 | Consensus on | Observers provided unequivocal | Authors concluded that the | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| 1997) | common problems in the diagnosis of suspected melanoma lesions among experts in melanoma pathology. | study. | pathologists.<br><br>1069 consecutive referral cases of submitted lesions during 3 yr period.<br><br>60% from small laboratories with up to 3 consultant pathologists.<br><br>2/3 of lesions from women; nearly 50% of patients ≤30 years.<br><br>In 8% of cases referring pathologists unable to make confident diagnosis; 14% melanoma was suspected; 12% differential diagnosis only had been formulated.<br><br>Comparison made in terms of over diagnosis (defined from perspective of clinical relevance including therapeutic consequences) including suspected melanoma; invasive melanoma; common acquired naevus; Spitz naevus; special type of naevus; dysplastic naevus or melanoma in situ.<br><br>and under diagnosis | classification. | diagnosis in 93% of cases.<br><br>Diagnostic difficulties most often encountered with Spitz naevi and dysplastic naevi. Although rate of over diagnosis and under diagnosis quite high, in majority of cases diagnosis of referring pathologist matched diagnosis of Observers.<br><br>Over diagnosis:<br>Of 151 lesions classified by referring pathologists as suspected melanoma, 55 lesions were over diagnosed: Common Acquired Naevus (11); Spitz Naevus (25); Other special type of naevus (8); Dysplastic Naevus (8); Melanoma in situ (3).<br><br>0f 158 lesions classified as “invasive melanoma” by referring pathologists; 22 considered benign by Observers: Common Acquired Naevus (3); Spitz Naevus (10); Other special type of naevus (4); Dysplastic Naevus (2); Melanoma in situ (3).<br><br>Under diagnosis:<br>Of 84 lesions classified by referring pathologists as Common Acquired Naevus, 12 considered by observers as “suspected melanoma” or invasive melanoma;<br><br>Numbers of under diagnosed lesions were:<br>Spitz naevus: 25 of 157;<br>Other special type of naevus: 7 of 54;<br>Dysplastic naevus: 44 of 176;<br>Melanoma in situ: 20 of 46. | high numbers of discordances reflect intrinsic difficulty of differential diagnoses in the selected material submitted.<br>Diagnostic difficulties most often encountered with Spitz naevi and dysplastic naevi.<br><br>*Observers diagnosed more cases of invasive melanoma in females than males compared with general population, possibly due to overall surplus of lesions from females submitted.*<br><br>*Percentage of invasive melanomas in Patients <30 years was high when compared to general population.*<br><br>*Cases submitted many with suspicion of malignancy but few with diagnosis of melanoma in situ.* | |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | defined as lesions classified as common acquired naevus; Spitz naevus; special type of naevus; dysplastic naevus; melanoma in situ; suspected melanoma; invasive melanoma .<br><br>**Holland** | | | | |
| (Wechsler *et al.* 2002) | To assess inter rater reliability in the diagnosis of malignant melanoma in children. | Retrospective study. | Observers: 8 (4 pairs) expert dermatopathologists (practised >10 years in academic dermatology and/or oncology centre).<br><br>85 slides of melanomas diagnosed in patients <17 years (one slide per case).<br><br>Slides classification:<br>1) Metastatic melanoma (Gold Standard) Mean age 12 years.<br>2) disease-free children with follow-up of <5 years; Mean age 12 years.<br>3) disease-free children with follow-up of ≥5 years; Mean age 11 years (Age p = 0.28)<br><br>As a control 35 unambiguous tumours selected (benign naevi | Concordance between pairs of experts. | Observers reviewed slides and classified into:<br>Melanoma; naevus (including Spitz naevus); or ambiguous tumours.<br><br>Category 1 slides (from children with metastatic melanoma) n=20 , concordance was weak to moderate; K (mean±SD) 37.7±13.1.<br><br>Category 2 slides (from disease-free children with follow-up <5 years) n=47, concordance was weak; K (mean±SD) 32.7±5.2.<br><br>Category 3 slides (from disease-free children with follow-up of ≥5 years) n=18, concordance was poor to moderate; K (mean±SD) 30.8±115.9.<br><br>Distribution of diagnosis differed widely among pairs of dermatopathologists (p < 0..001).<br><br>Control: 34 unambiguous case slides agreement among panel was perfect (K = 100%). | Authors concluded that study demonstrates the reliability of diagnosis of melanoma in childhood is poor, even when submitted to experts. To improve diagnosis reliability need to identify those morphologic criteria that will allow separation of metastatic cases from benign or ambiguous tumours. Diagnosis criteria should be documented.<br><br>*In some cases members of observer panel had been involved in making initial diagnosis of cases included.*<br><br>*No information on how slides selected.* | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | n=14; typical adult melanomas n=21).<br><br>**France** | | | | |

# Chapter 4 – Initial investigation, diagnosis, staging and management

## Introduction

Evidence on the role of GPs in the diagnosis of melanoma and NMSC was reviewed in chapter three, in the context of the role of GPs within skin cancer MDTs. Evidence on further aspects of skin cancer diagnosis and subsequent treatment is reviewed here.

## Diagnosis of skin cancer

### Dermatoscopy

#### The questions

*How effective is dermatoscopy in the diagnosis of skin cancer and pre-malignant lesions?*

*What effect does the experience of the operator have on the diagnostic accuracy of dermatoscopy, for skin cancer?*

#### The nature of the evidence

Five studies were identified, as follows:

- Three systematic reviews of good quality
- Two observational studies of fair quality

One observational study originates from the UK and the remaining four studies are one each from France, Italy, Austria and Australia. Applicability to the UK is therefore limited. All five studies are of the use of dermatoscopy by clinicians in the diagnosis of melanocytic skin lesions.

**Summary of the supporting evidence for the recommendations**

**Systematic review evidence is suggestive that dermatoscopy yields greater diagnostic accuracy than naked eye examination, although no effect has been found from the use of different dermatoscopic diagnostic algorithms. Observational study evidence suggests that dermatologists who use dermatoscopy 'can show improvement in performance, in terms of the malignant to benign ratio achieved in the diagnosis of melanocytic lesions. Observational study evidence also suggests that SIAscopy (where SIA = spectrophotometric intracutaneous analysis) may achieve favourable performance, compared to dermatoscopy, in the diagnosis of melanoma.**

**Systematic review evidence suggests that diagnostic accuracy of dermatoscopy is dependent upon the degree of experience of the operator.**

- The systematic review by Bafounta et al. (2001) found the sensitivity of dermatoscopy to have range 75 – 96% and specificity, range 79 – 98%. The odds ratio for diagnosis of melanoma by dermatoscopy was estimated as 76 (95%CI: 25 – 223) versus 16 (95%CI: 9 – 31) for naked-eye examination (p = 0.008).

- The observational study by Carli et al. (2004) found that dermatoscopy users showed statistically significant improvement over the study period in terms of malignant: benign ratio in the diagnosis of melanoma, with no significant improvement in nonusers. Dermatoscopy users were more likely to have diagnosed a melanoma tumour within a series of excised lesions, than nonusers.

- The systematic review by Kittler et al. (2002) found diagnostic accuracy for melanoma to be higher with dermatoscopy (odds ratio 4.0, 95%CI: 3.0 – 5.1) than without dermatoscopy (odds ratio 2.7, 95%CI: 1.9 - 3.4), although since the 95% confidence intervals overlap, the odds ratio values may be equal for dermatoscopy and non dermatoscopy melanoma diagnosis. There was no significant difference in diagnostic

accuracy arising from the use of different dermatoscopic diagnostic algorithms. Diagnostic accuracy of dermatoscopy significantly depended on the degree of experience of the examiners, with odds ratio 3.8 (95% CI: 3.3 – 4.3) for “experts” versus 2.0 (95% CI: 1.4 – 2.6) for non-experts (p = 0.001).

- The systematic review by Mayer et al. (1997) estimated the likelihood ratios for a positive diagnosis of melanoma by dermatoscopy as having range 2.9 – 10.3.

- The observational study by Moncrieff et al. (2002) found that use of SIAscopy had specificity of 80.1% and sensitivity of 82.7% for melanoma and concluded that the performance of SIAscopy compares favourably with dermatoscopy.

# EVIDENCE TABLE 4.1

***How effective is dermatoscopy in the diagnosis of skin cancer and pre-malignant lesions?***

***What effect does the experience of the operator have on the diagnostic accuracy of dermatoscopy, for skin cancer?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bafounta *et al.* 2001) | To assess the accuracy of dermatoscopic diagnosis of melanoma by experienced observers versus naked-eye clinical examination. | Systematic review with meta-analysis<br>Inclusion criteria relating to primary study design: good description of spectrum of melanoma lesions and lesions commonly confused with melanoma; blinded comparison of diagnostic tests with histologic findings; calculable statistics.<br><br>Articles involving dermatoscopic criteria for diagnosing pigmented skin lesions, dermatoscopy terminology, | 8 diagnostic comparison studies of 2,193 lesions, 328 of which were melanoma tumours.<br><br>**France** | Calculated or calculable specificity, sensitivity and likelihood ratios.<br><br>Summary receiver operating curves were constructed from individual sensitivity and specificity calculations to compare the discriminatory power of dermatoscopy with that of the naked eye.<br><br>No formal method for assessing heterogeneity.<br><br>Reference standard was | Sensitivity of dermatoscopy ranged from 75 – 96%, while specificity ranged from 79 – 98%. Dermatoscopy had a significantly higher discriminatory power than clinical examination. Odds ratios of 76 (95%CI: 25 – 223) for dermatoscopy versus 16 (95%CI: 9 – 31) for naked-eye examination (p = 0.008). The estimated positive likelihood ratios were 9 (95%CI: 5.6 – 19) and 3.7 (95%CI: 2.8 – 5.3) for dermatoscopy and naked eye examination while the estimated negative Likelihood ratios were 0.11 (95%CI: 0.05 – 0.18) and 0.27 (95%CI: 0.19 – 0.36). | Review methodology generally adequately described.<br><br>Influence of study characteristics on the diagnostic performance of dermatoscopy not addressed.<br><br>Reviewers conclude that for experienced users, dermatoscopy is more accurate than clinical examination for diagnosing melanoma in a pigmented skin lesion. | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | accuracy of diagnosis for a single type of pigmented skin lesion and accuracy of computerised image analysis were excluded. | | histopathology. | | | |
| (Carli *et al.* 2004) | To assess the impact of routine dermatoscopy use on the malignant/benign ratio in excised melanocytic lesions. | Case series. | 3053 melanocytic lesions (319 melanoma 10.4%) diagnosed and excised. 6 dermatologists divided into 2 groups according to their use of dermatoscopy in routine activity (n = 2 dermatoscopy users and n = 4 nonusers). Study period was divided into pre-dermatoscopy period (1997), a shift phase (1998) and a dermatoscopy period (1999-2001).<br><br>**Italy** | Malignant/benign ratio. | During the study period, malignant/ benign ratio improved in dermatoscopy users only (from 1:18 to 1:4.3, p = 0.037). No significant difference was found for nonusers (from 1:11.8 to 1:14.4). Dermatoscopy users were more likely to have a melanoma diagnosed within a series of excised lesions than nonusers, even taking into account potential confounders such as sex, age and study period by means of multivariate analysis (odds ratio 1.55, 95% CI 1.17-2.01). The % of 'problem' naevi over the total number of excised lesions was higher in dermatoscopy users than in nonusers (year 2001, 51.6% vs. 40.9%, p = 0.014). | Authors suggest that a more appropriate selection of pigmented lesions are referred to surgery as a result of the adoption of dermatoscopy in routine melanoma screening. | 3 |
| (Kittler *et al.* 2002) | To compare accuracy of melanoma diagnosis with and without dermatoscopy, to assess the influence of study characteristics on the diagnostic accuracy of dermatoscopy and to report summary estimates of the diagnostic accuracy by | Systematic review with meta-analysis No explicit inclusion criteria relating to primary study design.<br><br>Studies involving computerised image analysis were excluded. | 27 studies with 9,821 lesions examined.<br><br>**Austria** | Calculation of sensitivity and specificity of dermatoscopy. Where data available, log odds ratio and confidence intervals calculated. Summary receiver | Prevalence of melanoma was 1.6-60.8% (mean 28.3). Mean or median Breslow thickness reported in 15 studies 0.40 – 1.11mm (median 0.70).<br><br>13 studies directly compared accuracy of melanoma diagnosis with and without dermatoscopy:<br><br>Diagnostic accuracy for melanoma was significantly higher with dermatoscopy | No method for assessing validity reported.<br>Method of data extraction not stated.<br>Literature search limited to one data base and English and German, however references of retrieved articles were examined and grey literature sought. | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | combining data. | | | operating curves were constructed from individual sensitivity and specificity calculations to compare the discriminatory power of dermatoscopy with that of the naked eye.<br><br>Variation in diagnostic accuracy due to study characteristics was assessed by univariate and multivariate regression analyses. Threshold effect investigated.<br><br>Reference standard was histopathology. | (odds ratio 4.0, 95%CI: 3.0 – 5.1) than without (odds ratio 2.7, 95%CI: 1.9 - 3.4); an improvement of 49% (p = 0.001). For all 27 studies the results were similar; the odds ratios were 3.4 (95%CI: 2.9 - 3.9) and 2.5 (95%CI: 1.9 – 3.1) respectively (p = 0.03).<br><br>Diagnostic accuracy of dermatoscopy significantly depended on the degree of experience of the examiners. Odds ratio 3.8 (95%CI: 3.3 – 4.3) for "experts" v. 2.0 (95%CI: 1.4 – 2.6) for non-experts (p = 0.001) (expert not defined by reviewers). Dermatoscopy by untrained or less experienced examiners was no better than clinical inspection without dermatoscopy. Diagnostic performance improved when diagnosis made by group of examiners in consensus.<br><br>Univariate analysis of various diagnostic algorithms for dermatoscopy showed no significant differences in performance: odds ratio 3.6 (95%CI: 2.8 – 4.4) for pattern analysis, 3.2 (95%CI: 2.4 – 3.9) for ABCD rule and 3.1 (95%CI: 2.1 – 4.0) for scoring systems (p = 0.64). | Reviewers state that the results of most studies were potentially influenced by verification bias. This would result in a probable overestimation of sensitivity and underestimation of specificity.<br><br>Reviewers conclude that dermatoscopy improves the diagnostic accuracy for melanoma in comparison with inspection by the unaided eye. However, dermatoscopy requires sufficient training and cannot be recommended for untrained users. A consensus diagnosis involving 2 or more experts is recommended to yield the highest possible diagnostic accuracy. | |
| (Mayer 1997) | To assess the evidence that dermatoscopy improves the accuracy of diagnosis of melanoma in clinical practice. | Systematic review<br>Inclusion criteria for primary studies: studies comparing diagnostic accuracy of dermatoscopy with another method of clinical diagnosis; determination of the accuracy of dermatoscopic diagnosis over a large range of | 6 studies of 1,382 lesions. 3 studies used hand-held monocular dermatoscopes, 2 used binocular stereo microscopes and 1 study used both.<br><br>**Australia** | Specificity, sensitivity and positive likelihood ratios.<br><br>Meta-analysis and an estimation of a single summary statistic were considered inappropriate due to variability in sensitivity and specificity in clinical | Likelihood ratios for a positive diagnosis of melanoma by dermatoscopy ranged from 2.9 – 10.3. Studies comparing sensitivity and specificity of dermatoscopy to non-dermatoscopic diagnosis gave conflicting results. Dermatoscopy had 10-27% higher sensitivity than clinical diagnosis in 2 studies with the most clinically equivocal lesions. However, when sensitivity of clinical diagnosis was >84%, sensitivity of dermatoscopy was only slightly higher. One study of dermatologists with no training in dermatoscopy showed a | Insufficient detail in primary studies led to hampering of assessment of studies' internal and external validity.<br><br>Reviewers conclude that variability in the studies in methods, observers and types of pigmented lesions, and the lack of studies in primary care make the generalisability of results difficult. | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | pigmented lesions, including a spectrum of stages of melanoma and lesions commonly confused with melanoma.<br><br>Studies with no comparison group were excluded. | | diagnosis between studies, and the potential variability in the observers' ability to make diagnosis. Narrative review only.<br><br>Reference standard was histopathology. | significant decrease in sensitivity. | | |
| (Moncrieff *et al.* 2002) | 1. To identify features from SIAgraphs that may assist in the early identification of melanoma when compared with the histopathological examination from excision biopsy. | Observational study. | 348 lesions including 52 Melanoma tumours of varying sub-types and Breslow thicknesses (mean 1.52mm).<br><br>**UK** | Reliability and reproducibility of features. Sensitivity and specificity.<br><br>Receiver operator characteristic curves constructed for combinations of features. | Highly reproducible and reliable features were identified, with high specificity (80.1%) and sensitivity (82.7%) for melanoma. When analysed using ROC curves for combinations of SIAscopy features, performance compares favourably with dermatoscopy and revised 7-point checklist. | No indication of whether test and reference standards were measured independently. No indication of blinding of investigators carrying out each test to the results obtained from the other. | 3 |

**The question**

*What is the effect of providing training to clinicians in dermatoscopy in terms of diagnostic accuracy for skin cancer?*

**The nature of the evidence**

Five studies were identified, as follows:

- One RCT of poor quality.
- Three observational studies of fair quality
- One clinical guideline of good quality

One study is from the UK, two studies are from Austria, one study is from Italy and the RCT is from Australia. Applicability to the UK is limited.

The Australian RCT uses general practitioners as subjects. The other studies are of dermatologists. All of the studies address the diagnosis of pigmented lesions, including melanoma.

**Summary of the supporting evidence for the recommendations**

**Evidence from observational studies suggests that adequate training is necessary in order for dermatologists to be able to make accurate diagnoses using dermatoscopy, but that diagnostic accuracy can be improved through the use of dermatoscopy for pigmented lesions, including melanoma. The same level of evidence suggests that the use of dermatoscopy produces greater diagnostic performance in dermatologists who are familiar with its use, but impairs diagnostic performance in dermatologists who are untrained in its use. There is also observational study evidence that the effect of training in dermatoscopy is stronger among dermatologists who see a greater frequency pigmented lesions. RCT evidence suggests that provision of training to GPs in the diagnosis of melanoma can increase their diagnostic performance, both using clinical signs and dermatoscopy.**

**Evidence based guidelines from within the UK recommend that clinicians using hand held dermatoscopy should be appropriately trained in its use.**

- The non-randomised, intervention study by Binder et al. (1997) found that after training, the diagnostic performance of previously untrained dermatologists for melanocytic lesions significantly increased, in dermatoscopy.

- The non-randomised, intervention study by Binder et al. (1995) concluded that the introduction of dermatoscopy increases diagnostic performance with regard to melanoma by dermatologists formally trained in dermatoscopy, but may decrease diagnostic ability in dermatologists not formally trained in the technique.

- Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that clinicians using hand held dermatoscopy should be appropriately trained.

- The non randomised intervention study by Stanganelli et al. (1999) found that the diagnostic performance of dermatologists with regard to pigmented skin lesions significantly increased after the provision of training. The percentage detection rate for melanoma was 55% pre training and 72% post training.

- The RCT by Westerhoff, McCarthy, and Menzies (2000) found that following a brief training intervention, there was a significant improvement in both clinical diagnosis of melanoma and in diagnosis of melanoma using dermatoscopy. The improvement was significantly larger for the use of dermatoscopy compared to clinical diagnosis.

# EVIDENCE TABLE 4.2

***What is the effect of providing training to clinicians in dermatoscopy in terms of diagnostic accuracy for skin cancer?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Binder *et al.* 1997) | To determine the effects of short formal epiluminescence microscopy (ELM) training on diagnostic performance. | Non randomised, 'before and after' intervention study. | 11 previously untrained dermatologists.<br><br>Sample set of 100 image-pairs of randomly selected malignant pigmented skin lesions photographed with (ELM) and without oil immersion (surface microscopy SM) presented by slide projection before and after training (9 hours of teaching on 3 consecutive days).<br><br>**Austria** | Diagnostic performance.<br><br>Diagnostic performance was described in terms of areas under ROC curves, which were calculated for each of the participants before and after training and for both methods (SM vs. ELM). | Without training 8/11 participants performed less accurately with ELM, with an average loss of accuracy of 1.3%.<br><br>After training, accuracy with ELM was significantly better than with SM in 7/11 participants, with an average improvement of 3.8% (p = 0.015)<br>Diagnostic performance by SM increased after training by 3.3% in all participants (p = 0.04)<br>Diagnostic performance by ELM after training by 8.4% in all participants (p = 0.001). | Slides analysed, not patients<br>Small number of participants. | 3 |
| (Binder *et al.* 1995) | To determine whether the clinical diagnosis of pigmented skin lesions is significantly improved using ELM and whether ELM –trained individuals and dermatologists not | Non randomised, 'before and after' intervention study. | 6 ELM experts and 13 ELM non-experts.<br><br>Sample set of 240 image-pairs of randomly selected | Diagnostic performance.<br><br>Diagnostic performance of ELM experts and non-experts using | Using the ELM technique ELM experts reach a substantially better intra-observer agreement than non-experts (median kappa, 0.56 vs. 0.36). The inter-observer agreement was markedly increased in the ELM experts group (average gain, 7%) but decreased in the | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | trained n this technique benefit equally. | | malignant Pigmented skin lesions photographed with (ELM) and without oil immersion (surface microscopy SM) presented by slide projection.<br><br>**Austria** | ELM vs. SM estimated by intra-observer and inter-observer agreement by K statistics and sensitivity and specificity of diagnostic performance. | ELM non-experts group (average loss, 6%). Sensitivity of diagnosis was significantly increased in the ELM experts group (average gain, 10%), but decreased in the non-experts group (average loss, 10%). Specificity of diagnosis in the ELM experts group, both with and without oil immersion was (0.91) and was improved by ELM in the non-experts group (0.77 vs. 0.85).<br><br>ELM technique appears to increase sensitivity in formally trained dermatologists, but may decrease diagnostic ability in dermatologists not formally trained. | | |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**Scotland** | Recommendations for practice. | Clinicians using hand held dermatoscopy should be appropriately trained. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |
| (Stanganelli *et al.* 1999) | To determine the effect of training on diagnostic accuracy using ELM. | Non randomised, 'before and after' intervention study. | 83 dermatologists out of a possible 223 attending the workshops.<br><br>30 ELM images of Pigmented skin lesions independently diagnosed before and after 1 day workshop on ELM.<br><br>**Italy** | Diagnostic performance: Number of Pigmented skin lesions unclassified, number of melanomas, melanocytic naevi and non-melanocytic lesions (lesions correctly identified as such); positive predictive | Compared with pre-training, average % of exact diagnosis increased significantly for all Pigmented skin lesions (melanoma, 72% vs. 55%; melanocytic naevi, 68% vs. 64%; non-melanocytic lesions, 67% vs. 58%; total lesions combined, 69% vs. 60%). Before and after training accuracy were independent from professional sector and years of experience but were greater among subjects reporting > 20 Pigmented skin lesions per week compared with < 10 Pigmented skin lesions. Routine use of ELM was | Participants self-selected to participate on course.<br>Low response rate.<br>Some already experienced in ELM use. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | value for melanoma; total number of exact diagnoses. | associated with a slight advantage in before training accuracy. | | |
| (Westerhoff *et al.* 2000) | To determine whether GPs could improve accuracy of diagnosis of melanoma using surface microscopy after a short education intervention. | RCT | 74 GPs :<br>34 in each arm of study.<br><br>Inclusion criteria: no formal training with surface microscopy and no use in clinical practice.<br><br>Intervention: Provision of text book about recognition of surface microscopic features for diagnosing invasive melanomas. 1 hour presentation on surface microscopy, including a quiz with images of 25 different Pigmented skin lesions.<br><br>**Australia** | Correct diagnosis. | Following training there was a significant improvement in the post-test vs. pre-test in both clinical melanoma diagnosis (62.7% vs. 54.6%; P = 0.007) and surface microscopy melanoma diagnosis (75.9% vs. 57.8%; P = 0.000007).<br><br>No difference was found in the control group between the post-test vs. pre-test clinical melanoma diagnosis (53.7% vs. 50.6%; P = 0.21) or the surface microscopy melanoma diagnosis (54.8% vs. 52.9%; P = 0.56).<br><br>Following training there was a significant improvement in the diagnosis of melanoma using surface microscopy vs. clinical diagnosis (75.9% vs. 62.7%; P = 0.000007), which was absent in the control group (54.8% vs. 53.7%; P = 0.59).<br><br>No significant difference was found in clinical vs. surface microscopy post-test results for non-melanoma PSL in either the intervention group or control group.<br><br>Improvement in the sensitivity for the diagnosis of melanoma with surface microscopy was seen without a decrease in specificity. | Recruitment liable to bias<br>No information on randomisation.<br><br>No information about whether investigators were blinded.<br><br>No information given about participants to be able to assess similarity at baseline.<br><br>No information given about drop-outs. | 1- |

## Teledermatology

### The questions

*In patients with skin cancer, is teledermatology effective in terms of MDT working?*

*In patients with suspected skin cancer, is teledermatology effective in terms of accuracy?*

*In patients with suspected skin cancer, is teledermatology effective in terms of accessibility / time?*

### The nature of the evidence

No studies were identified which evaluate teledermatology with MDT working as an outcome measure. For the other two questions, thirteen studies were identified as follows:

- Four RCTs, one of good quality, one of fair quality and two of poor quality
- Nine observational studies of fair quality

Ten studies are from the UK and one study each is from the US, Holland and New Zealand. Applicability to the UK is good. All of the studies relate to patients requiring referral to dermatology services.

### Summary of the supporting evidence for the recommendations

**RCT evidence suggests that significantly greater diagnostic and management plan concordance between physicians is achieved by face-to-face consultation, compared to the use of store-and-forward teledermatology, but that teledermatology can reduce the time to definitive treatment compared with traditional referral. Audit data from the UK indicates that GPs report quicker referral of dermatology patients, than those referred by traditional methods. RCT evidence suggests that store-and-forward teledermatology and real time**

**teledermatology are equally effective for clinical diagnosis, and that teledermatology can avoid the need for patients making further clinic visits. Evidence from a further RCT suggests that approximately half of dermatology patients can be managed in primary care through the use of teledermatology.**

**There is observational study evidence of high diagnostic concordance between teledermatology consultations and face-to-face consultations, with rates reported with range 54% to 77%.**

- The RCT by Bowns et al. (2003) compared teledermatology with face-to-face skin examination in patients with skin lesions. Concordance of diagnosis and management plan was measured for each group with an independent face-to-face skin examination. There was significantly greater diagnostic and management plan concordance arising in patients randomised to face-to-face skin examination than those randomised to teledermatology, with no difference detected between the two groups for patient satisfaction.

- The case series study by Du Moulin et al. (2003) found that there was full concordance between store-and-forward and face-to-face diagnoses in 54% of patients referred to dermatologists.

- The case series study by Gilmour et al. (1998) which compared face-to-face consultations and teleconsultations found that there was diagnostic concordance in 59% of cases and that dermatologists were able to make a definitive diagnosis by face-to-face consultations in significantly more cases than by teleconsultations.

- The case series study by Lewis et al. (1999) of store-and-forward teledermatology found that there was clinical agreement between teledermatologist and face-to-face dermatologist in 93% of cases, with sensitivity of 88% and specificity of 80%.

- The audit by Linck et al. (2003) found that 40% of patients referred for teledermatology were diagnosed, prioritised and triaged within 24 hours

of referral, 83% within 7 days and 97% within 21 days. Almost 90% of GPs thought telemedicine provided a quicker diagnosis and overall patient satisfaction with teleconsultation was 97%.

- The case series study by Loane et al. (1998) found that correct diagnostic concordance between store-and-forward teledermatology and face-to-face consultation was reached in 67% of cases.

- The RCT by Loane et al. (2000a) compared two types of teledermatology (live videoconferencing and sending of still photographic images) with traditional outpatient consultation, as methods for GPs to refer patients to dermatologists. The dermatologist requested a subsequent hospital appointment for 69% of patients examined by the still image method, compared to 46% of patients examined by videoconferencing and 45% of patients examined in person.

- The case series study by Lyon and Harrison (1997) evaluated a digital imaging system for use by trainee dermatologists and demonstrated an agreement rate of 95% for non-operative referrals and 94% for operative referrals.

- The case series study by Mallett (2000) found that store-and-forward teledermatology when used by GPs resulted in 89% diagnostic concordance with dermatologists for skin lesions.

- The case series study by Oakley et al. (1997) found that the use of a video conferencing system resulted in 75% of cases being correctly diagnosed using telemedicine.

- The case series study by Taylor et al. (2001) found that concordance between store-and-forward teledermatology and face-to-face consultation was 77% and that by using teledermatology, consultants recommended fewer urgent appointments.

- The RCT by Whited et al. (2002) which compared teledermatology with usual referral care found that patients in the teledermatology group reached a time to initial definitive intervention significantly sooner than did those patients randomised to usual care, and that teledermatology patients were significantly more likely to avoid the need for a further clinic visit compared with control patients.

- The RCT comparing real time teledermatology with outpatient dermatology by Wootton et al. (2000) found no major differences in the reported clinical diagnoses between groups. In the teledermatology group, 54% of patients were managed within primary care and 46% required at least one hospital appointment.

# EVIDENCE TABLE 4.3

***In patients with suspected skin cancer, is teledermatology effective in terms of accuracy?***

***In patients with suspected skin cancer, is teledermatology effective in terms of accessibility/time?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bowns *et al.* 2003) | To assess the equivalence of store-and-forward teledermatology and face-to-face consultation in setting a management plan for new adult outpatient referrals. | RCT<br><br>Intervention:<br><br>Referral made to consultant using 1 or more digital still images and a structured electronic referral and reply.<br><br>Control group managed by traditional outpatient appointment.<br><br>All cases were seen face-to-face by a second, independent consultant to | 92 telemedicine cases and 72 control cases recruited from 8 general practices which referred patients to a single hospital.<br><br>**UK** | Concordance between clinicians for diagnosis and management plan.<br><br>Patient and GP satisfaction, assessed by survey and interview; consultants' views by interview. | Diagnostic concordance:<br>Telemedicine cases 51/92: 55%<br>Controls 57/72: 79%<br>(p = 0.003).<br><br>Management concordance:<br>Telemedicine cases 51/92: 55%<br>Controls 60/72: 83%<br>(p = 0.0003).<br><br>53 telemedicine cases were judged to also require a face-to-face consultation, mainly to establish a diagnosis and treatment plan.<br><br>No difference was detected between 2 groups for patient satisfaction. Clinicians had a number of concerns and felt future role to be limited. | Abstract only – unable to assess methodological quality.<br><br>Blinding of intervention not possible which will introduce bias. | 1 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | give a second opinion for comparative purposes. | | | | | |
| (Du Moulin *et al.* 2003) | To examine the reliability of diagnoses made using store-and-forward teledermatology. | Case series. | 117 patients, referred by 18 general practitioners for diagnosis of a skin condition by one teledermatologist.<br><br>Compared with face-to-face diagnosis by one of 8 other dermatologists; compared with biopsy if appropriate.<br><br>**Netherlands** | Diagnostic concordance. | There was full concordance between store-and-forward and face-to-face diagnoses in 57 of 106 cases (54%); in 10 cases (9%) there was overlap between the differential diagnoses provided by the teledermatologist and the face-to-face consultant.<br><br>In malignant or pre-malignant diagnoses, there was concordance in 5/6 cases. | | 3 |
| (Gilmour *et al.* 1998) | To undertake a systematic comparison of face-to-face consultations and teleconsultations performed using low-cost videoconferencing equipment (PHASE 1). | Multi-centre case series (2 in Manchester and 1 in Northern Ireland). | 155 diagnoses from a sample of 126 patients.<br><br>Each patient had a teleconsultation followed by a face-to-face consultation.<br><br>In one site (Northern Ireland) these consultations were by the same dermatologist.<br><br>**UK** | Diagnostic concordance, management plans and patient and doctor satisfaction. | Diagnostic concordance was achieved in 59% of cases. Teleconsultations missed a secondary diagnosis in 6% of cases and were unable to make a useful diagnosis in 11% of cases. Incorrect diagnoses were made by the teledermatologist in 4% of cases. Dermatologists were able to make a definitive diagnosis by face-to-face consultations in significantly more cases than by teleconsultations (P = 0.001). Where both types of consultation resulted in a single diagnosis there was a high level of agreement (kappa = 0.96, 95% CI 0.91-1.00).<br><br>Overall follow-up rates from both types of consultation were almost identical. 50% of patients seen could have been managed using a single video conference teleconsultation without any requirement for further specialist intervention.<br><br>Patients reported high levels of satisfaction with the teleconsultations. General practitioners reported that 75% of the teleconsultations were of educational benefit. | Authors conclude that the study illustrates the potential of telemedicine to diagnose and manage dermatology cases referred from primary care.<br><br>Specifically for tumours:<br>Total concordance in 13/20 lesions; teledermatologist listed 2-3 closely related diagnoses' face-to-face dermatologist a | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | single diagnosis in a further 5/20 cases.<br>In 1 case no useful diagnosis could be made by teledermatologist and in 1 case there was a missed secondary diagnosis by teleconsultation. | |
| (Lewis *et al.* 1999) | To evaluate a low-cost store-and-forward teledermatology system using digital images for the remote diagnosis and management of skin tumours. | Case series. | 141 patients referred for specialist opinion.<br><br>Diagnosis made by clinical examination and digital image taken, which was then assessed by a different dermatologist.<br><br>**UK** | Concordance. | ROC analysis revealed clinical agreement between teledermatologist and face-to-face dermatologist in 93% of cases.<br>Sensitivity: 88%<br>Specificity 80% | Assessment appears to be of the benign/malignant nature of lesions, rather than a precise diagnosis.<br>No details of diagnoses given. | 3 |
| (Linck *et al.* 2003) | To conduct a service evaluation of store-and-forward teledermatology. | Audit based upon data collected via questionnaires, interviews and routinely collected activity data. | Dermatology patients.<br><br>**UK** | Time to diagnosis.<br><br>GP and patient satisfaction. | 137 referrals of 136 patients with a consultant dermatologist in a 12-week period.<br><br>40% patients referred for teledermatology were diagnosed, prioritised and triaged within 24 hours of referral, 83% within 7 days and 97% within 21 days.<br><br>Teledermatology avoided the need for 75 face-to-face consultations with a consultant dermatologist over the 12-week period.<br><br>**GP satisfaction (40% response rate):**<br>Almost 90% thought telemedicine provided a quicker diagnosis. However, some found the service was not quicker, particularly those referring to the new site.<br>Quality of diagnosis:<br>"As good as" a face-to-face consultation 57%<br>Uncertain 33%<br>Quality of patient management:<br>"As good as" a face-to-face consultation 57% | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Uncertain 44%<br><br>**Patient satisfaction (32% response rate):**<br>Prefer to see dermatologist in person 41%<br>If given a choice between telemedicine and a few months' wait, would rather use telemedicine 97%<br>Overall satisfaction with teleconsultation 97% | | |
| (Loane *et al.* 1998) | To assess the effectiveness of real time teledermatology in Northern Ireland. | Case series. | 351 patients with 427 diagnoses Each patient had a teleconsultation followed by a face-to-face consultation on the same day (64% seen by same consultant in each case).<br><br>**UK** | Diagnostic concordance. | Correct correlation 285 (67%)<br>Differential correlation 67 (16%)<br>FTF differential 6 (1%)<br>No diagnosis 26 (6%)<br>Missed diagnosis 17 (4%)<br>Wrong diagnosis 26 (6%)<br><br>Diagnostic correlation decreased when patient seen by a different dermatologist at the face-to-face consultation. | Paper also reports results for concordance for management plans – but this is also reported in paper below (different patient numbers).<br><br>No details of diagnoses given. | 3 |
| (Loane *et al.* 2000b) | To assess the clinical effectiveness and cost-effectiveness of both real-time and store-and-forward teledermatology compared with conventional outpatient dermatological care. | RCT<br>Study group: 102 received teledermatology consultation; 96 of which also referred using store-and-forward<br>Control group: 102 received traditional outpatient consultation. | 204 general practice patients from 4 health centres (two urban, two rural) requiring referral to dermatology services at 1 of 2 regional hospitals.<br><br>**UK** | Reported clinical outcome of initial consultation, primary care and outpatient re-attendance data, (and cost-benefit analysis of both methods of delivering care). | There were no differences in the reported clinical outcomes of real-time teledermatology and conventional dermatology. Of those randomised to the real-time teledermatology consultation, 46% required at least one subsequent hospital appointment compared with 45% of those randomised to the conventional outpatient consultation. In contrast, the dermatologist requested a subsequent hospital appointment for 69% of those seen by store-and-forward teledermatology. | Sample size calculations performed. Suitable concealed randomisation. Blinding of treatment not possible – not known whether analysis of data performed blind.<br><br>Insufficient detail of patients given to assess similarity at baseline of two groups.<br><br>Cost-effectiveness element not reported/appraised here. | 1- |
| (Lyon & Harrison | To investigate the | Case series. | 100 patients seen | Diagnostic | Agreement for 95% non-operative referrals (n=38) and 94% operative | Authors suggest that | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| 1997) | diagnostic usefulness of a digital imaging system for use by trainee dermatologists operating clinics at sites remote from consultants. | | by a trainee. Images presented to dermatologist consultant together with one-sentence summary. Image-based diagnosis recorded. Compared with final histological diagnosis or clinical progress as assessed on subsequent examination by same consultant.<br><br>**UK** | accuracy. | referrals (n=62).<br><br>No malignancies were missed. | such a system is particularly important for the specialist registrar given the BAD recommendation for dermatology training that the trainee should have "ready access to support and advice from a consultant at all times". | |
| (Mallett 2000) | To evaluate a store-and-forward teledermatology communications process, using digital images attached to emails. | Case series. | 8 GP practices (precise number of GPs not given), making referrals for 81 patients to 1 of 2 dermatologists generating 185 images.<br><br>**UK** | Image quality; ability to make a diagnosis; diagnostic accuracy compared with diagnoses made at face-to-face consultations. | Image quality:<br>Good 28%<br>Fair 58%<br>Unclear 14%<br><br>Diagnosis ability:<br>43 cases (53%)<br><br>Diagnostic accuracy of 38 telediagnoses:<br>Rashes 94% match<br>Lesions 89% match | | 3 |
| (Oakley *et al.* 1997) | To determine the accuracy of a video conferencing system in diagnosis of dermatological disorders. | Case series. | 104 patients with 135 dermatological conditions; initially assessed by telemedicine and subsequently by face-to-face consultation by same dermatologist.<br><br>**New Zealand** | Diagnostic accuracy. | 75% of conditions were correctly diagnosed using telemedicine. In a further 7% a differential diagnosis was made. In 12% the diagnosis was incorrect and in 3% no diagnosis could be made. 4% of diagnoses were made only when the patient was seen face-to-face. | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Taylor *et al.* 2001) | To evaluate the role of telemedicine in the dermatology outpatients department of a district general hospital. | Case series. | 194 patients seen by 1 of 2 dermatologists for face-to-face consultation. Images taken at the time reviewed 13 months later by same dermatologists for a provisional diagnosis and assessment of how urgent an appointment would have been made.<br><br>Relevant diagnoses:<br>Benign pigmented nevus 43<br>BCC 9<br><br>**UK** | Diagnostic concordance. | Concordance achieved in 77% cases. Using the system, consultants recommended fewer urgent appointments (32% compared with 64%) and felt that in 31% of cases the patient did not need to be seen. In 15% of these cases (5% of the total), however, their diagnosis differed significantly from that of the consultant who saw the patient. Had the system been in use, 14% of patients conventionally assigned a non-urgent appointment would have been seen urgently. | Authors not impressed with reliability of software (6 cases could not be viewed), or its ease of use (about 1 hour to view 20 cases). | 3 |
| (Whited *et al.* 2002) | To determine whether a teledermatology consult system, using store-and-forward digital imaging technology, results in patients achieving a shorter time from referral date to date of initial definitive intervention when compared to a traditional referral process. | RCT<br>Study group: 135 patients received teledermatology (digital images and a standardised history).<br><br>Control group: 140 patients received usual care (text-based electronic consult request). | 275 patients being referred to a dermatology department of hospital from primary care clinics.<br><br>No details about specific diagnoses.<br><br>**US** | Time to initial definitive intervention (defined as the time between referral date and the date the patient was scheduled for a clinic visit for those patients that the consultant requested a clinic-based evaluation, or the time between | Patients in the study group reached a time to initial definitive intervention significantly sooner than did those patients randomised to usual care (median 41 days versus 127 days, $p = 0.0001$, log-rank test). Additionally, 18.5% of patients in the study arm avoided the need for a dermatology clinic-based visit compared to zero patients avoiding a dermatology clinic visit in the usual care arm of the study ($p < 0.001$, z-test). | Method of randomisation unclear. Research assistants blinded<br>No sample size/power calculations<br>No significant differences between the 2 groups at baseline<br>All participants followed up.<br>Only 35% eligible patients recruited. However, time to a scheduled clinic visit did not differ | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | Exclusion criteria: Conditions considered emergent and requiring prompt attention. | | referral date and the date the consult was answered by the consultant if a clinic visit was not required). | | between eligible non-enrolled patients and enrolled usual care patients.<br><br>Authors conclude that teledermatology consult systems can result in significantly shorter times to initial definitive intervention for patients compared to traditional consult modalities, and, in some cases, the need for a clinic-based visit can be avoided. | |
| (Wootton *et al.* 2000) | Comparison of real time teledermatology with outpatient dermatology in terms of clinical outcomes, cost-benefits, and patient re-attendance. | RCT<br>Minimum follow-up 3 months<br>Study group: 102 received teledermatology consultation<br>Control group: 102 received traditional outpatient consultation. | 204 general practice patients from 4 health centres (two urban, two rural) requiring referral to dermatology services at 1 of 2 regional hospitals.<br><br>**UK** | Reported clinical outcome of initial consultation, primary care and outpatient re-attendance data, (and cost-benefit analysis of both methods of delivering care). | No major differences were found in the reported clinical outcomes of teledermatology. In study group, 55 (54%) were managed within primary care and 47 (46%) required at least one hospital appointment. In control group, 46 (45%) required at least one further hospital appointment, 15 (15%) required general practice review, and 40 (39%) no follow-up visits. Clinical records showed that 42 (41%) study group patients attended subsequent hospital appointments compared with 41 (40%) patients seen conventionally. | Sample size calculations performed. Suitable concealed randomisation. Blinding of treatment not possible – not known whether analysis of data performed blind.<br><br>Insufficient detail of patients given to assess similarity at baseline of two groups.<br><br>Cost-effectiveness element not reported/appraised here. | 1- |

**The question**

*In patients with skin cancer, is teledermatology effective in terms of patient satisfaction?*

**The nature of the evidence**

Five studies were identified as follows:

- One systematic review of poor quality
- One RCT of good quality
- Two observational studies, one of poor quality and one of fair quality
- One expert review of fair quality

Four studies are from the UK and one study is from the US. Applicability to the UK is good. All studies, at least in part, are of patients for whom telemedicine was used in the dermatology setting.

**Summary of the supporting evidence for the recommendations**

**Systematic review, RCT and observational study evidence consistently suggests high levels of patient satisfaction with teledermatology, citing benefits as increased accessibility to services, less need for travel and reduced waiting times. There is some evidence that some patients are concerned that contact with clinicians may be reduced. One randomised control trial demonstrated no difference in patient satisfaction arising from teledermatology versus traditional dermatological management, although satisfaction was high in both groups.**

- The systematic review by Mair and Whitten (2000) found that patients found teleconsultations acceptable, with advantages reported as increased accessibility of specialist expertise, less need for patients to travel and reduced waiting times. Some concern was expressed about teledermatology, relating to communication between provider and client.

- The cross sectional survey by Qureshi and Kvedar (2003) found that over half of patients would consider seeking an opinion from their physician or sending images of their skin to their clinician using a secure internet connection from their home computer.

- The case series study by Savill and Freeman (2004) found that patients were not intimidated by teledermatology technology and many felt that as a result of teledermatology, they were more involved in their own treatment and care planning.

- The expert review by Collins, Nicolson, and Bowns (2000) found that patients were largely satisfied with real time teledermatology and that younger patients were more willing to accept the new technology.

- The RCT undertaken by Collins, Walters, and Bowns (2004) found no significant difference between teledermatology and control groups for satisfaction with care ($p = 0.16$) or satisfaction with management of the skin problem ($p = 0.59$), and satisfaction in both groups was generally high. Of the telemedicine patients, 85% indicated that they would use the system again.

# EVIDENCE TABLE 4.4

***In patients with skin cancer, is teledermatology effective in terms of patient satisfaction?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Mair & Whitten 2000) | To review research into patient satisfaction with teleconsultation, specifically clinical consultations between healthcare providers and patients involving real time interactive video. | Systematic review of randomised and non-randomised studies of healthcare interventions involving teleconsultations, specifically those between healthcare providers (from any discipline) and patients that involved the use of real time interactive video. The following types of teleconsultation: psychiatry (child and adult); dermatology; multi-speciality; emergency medicine; oncology; hospice; family | 32 studies (including one RCT, 2 studies in which patients were randomly selected and one case-control study) were included (at least 2315 patients).<br><br>**UK** | Quality of evidence about patient satisfaction, principally overall satisfaction with the telemedicine service but also including levels of satisfaction with communication via this medium, telemedicine consultations compared with face-to-face traditional consultations, and technical performance and patients' willingness to use telemedicine in future. | Firm conclusions were limited by methodological flaws of included studies (mainly low sample sizes, context and study designs). It appeared that patients found teleconsultations acceptable; noting definite advantages particularly increased accessibility of specialist expertise, less travel required, and reduced waiting times. Some disquiet was expressed about this mode of delivery, particularly relating to communication between provider and client. | Comprehensive searching (although restricted to English language which may introduce language bias)..<br><br>Limited details of the primary studies were included in the text and results from primary studies were not reported in the text of the review. No details were given of methods used to select primary studies, assess validity or extract data. No comment was made on any heterogeneity among studies. | 1- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | practice consultations; primary care consultations; otolaryngology; diagnosis of speech and language disorders; home healthcare; home nursing; orthopaedic consultations; and patients with Parkinson's disease<br>1966 – 1998. | | | | | |
| (Qureshi & Kvedar 2003) | To evaluate patient knowledge of, attitudes toward and use of technologies that enable implementation of patient participation in telemedicine, specifically teledermatology. | Cross sectional survey of 430 dermatology outpatients. | Patients attending dermatology outpatient clinics.<br><br>**US** | | Two thirds of participants owned computers at home with Internet access, one in five owned digital cameras and 18% were able to transfer images using this technology. More than half would consider seeking an opinion from their physician or sending images of their skin to their clinician via a secure internet connection. The authors conclude that dermatology outpatients seem to be accepting of and technologically capable of participating in teledermatology. | Study assesses the potential for and participation in teledermatology from the patients' home environments.<br><br>Study does not corroborate diagnoses, co-morbidity or patient demographics. The response rate was 20%. | 3 - |
| (Savill & Freeman 2004) | to examine the use of low cost, PC based video conferencing equipment for teledermatology and educational purposes in rural Mid Wales. | Case series.<br><br>The Hospital Specialist (Consultant Dermatologist) held a real time teleconsultation with the General Practitioner and patient at their local surgery, | Patients visiting their GP for dermatological reasons.<br><br>**UK** | | **Patient satisfaction**<br>Only one patient out of the 75 completing questionnaires would opt for a traditional face-to-face consultation in the future largely due to a reduction in waiting time. Patients were not intimidated by the technology and many positively enjoyed the experience as they felt that they were more involved in their own treatment and care planning.<br><br>**Clinician satisfaction**<br>The participating clinicians saw benefits in reduced travelling and waiting times, skills transfer, reduced referral rates and improved teaching and audit capabilities. | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | followed by a face-to-face appointment at the GP surgery with the same Specialist four days later. | | | Authors report that possibly the most important aspect of the intervention was the shared consultation and its benefits. Amongst these were :-<br>a) improved communication between those involved in the teleconsultation,<br>b) the patient's perception that they were in receipt of an individualised service,<br>c) increased access to a Specialist's skills.<br>Other subsidiary findings were:-<br>a) the stored images enabled the patient's condition to be monitored and compared over a period of time,<br>b) nurses were also able to bring their patients for a shared consultation with the dermatologist,<br>c) using the technology for teledermatology encouraged clinicians to consider other clinical uses. | | |
| (Collins *et al.* 2000) | To provide an overview of telemedicine and patient satisfaction based upon published literature. | Expert review. | Various populations in primary studies.<br><br>**Review undertaken in the UK.** | Study reviews patient satisfaction and also problems related to its measurement. | Primary studies indicate that patients are largely satisfied with 'real time' teledermatology and younger patients are more willing to accept the new technology. Author notes that patients may under report dissatisfaction, that many studies are small and exploratory in nature and recommends that further research be undertaken. | | 4 |
| (Collins *et al.* 2004) | To measure patient satisfaction with a specialist dermatological opinion and further management obtained by teledermatology compared with the same obtained by traditional outpatient consultation. | RCT with 208 patients: 111 in telemedicine group and 97 in control group. Assessment made by questionnaire for all participants and by interview in 30 participants. | Patients aged 16 years or over requiring referral to a Consultant Dermatologist for a range of conditions: rashes, hair loss, lesions and others/not known.<br><br>**UK** | Questionnaire explores interpersonal aspects of healthcare (all participants). Interview explored subjective perceptions and satisfaction in 30 participants: 12 men/18 women i.e. 20 from teledermatology group and 10 from control group). | **Quantitative results:** No significant difference was found between teledermatology and control groups for satisfaction with care (p = 0.16) or satisfaction with management of the skin problem (p = 0.59). Satisfaction in both groups was generally high. Of the telemedicine patients: 85% would use the system again, 38% expressed a preference for face-to-face consultation, 40% said that something would be missing if they did not see the dermatologist in person and 76% would prefer teledermatology to a few weeks wait to see the dermatologist in person.<br><br>**Qualitative findings:** There was little difference in satisfaction between the two groups and satisfaction was high in both groups. Factors accounting for satisfaction were:<br>• diagnosis and cure<br>• Information and explanations<br>• Patients being taken seriously<br>• Individualised care<br>• Short waiting time for an appointment and treatment.<br>Authors conclude that the above list are important for patient | 71% response rate to questionnaire (n = 148: 80 from teledermatology group and 68 from control group). | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | satisfaction, regardless of modality. | | |

**The question**

*In patients with suspected skin cancer, is teledermatology effective in terms of cost?*

**The nature of the evidence**

Ten studies were identified as follows:

- Two systematic reviews, one of good quality and one of fair quality
- Three RCTs of fair quality
- Five observational studies of fair quality

Three studies are from the UK. Two studies are form the US and one study each is from Norway, Hong Kong, Canada, Finland and New Zealand. Applicability to the UK is likely to be low. All studies are of patients for whom teledermatology was used, where one systematic review was of telemedicine, including teledermatology.

**Summary of the supporting evidence for the recommendations**

**There is little high quality evidence to suggest that teledermatology is more cost effective than conventional care, and observational studies in different countries report very variable results on the cost effectiveness of teledermatology.**

**Two systematic reviews suggest that there is no consensus from the evidence provided from primary studies on whether teledermatology is more cost effective than traditional management of dermatology patients. However one of these reviews provides evidence that teledermatology may provide a cost saving to patients with longer journeys to dermatology services. RCT evidence from the UK suggests that teledermatology is generally not cost effective compared with conventional care, but that teledermatology may be cost effective where travel distances to dermatology services are greater than 78km. RCT evidence from New Zealand suggests that teledermatology is**

**comparable in terms of cost effectiveness to traditional care, with most savings benefiting patients.**

- The retrospective case series study by Bergmo (2000) found that real time teledermatology was cheaper than traditional referral in Norway, where patients may be 800km from dermatology services.

- The retrospective case series study in the US by Burgiss et al. (1997) found that the average cost of care for treating a patient with a dermatology condition, based upon all patients seen during a period of 8 months prior to the introduction of teledermatology was $294, compared with $141 for the 6 months after the introduction of teledermatology.

- The case series study in Hong Kong by Chan et al. (2000) found that teledermatology incurred a cost per patient of 18% of that associated with patients travelling to see dermatologists and that between 48 and 145 patients needed to be seen by teledermatology to offset the maintenance costs of the teledermatology system.

- The systematic review by Hailey, Roine, and Ohinmaa (2002) found that teledermatology was associated with increased costs to healthcare providers, though not to patients, particularly those with longer journeys.

- The case series study by Lamminen et al. (2000) found teledermatology to be marginally more expensive to face to consultation, but reported economic benefits arising from a reduced need for travel.

- The case series study by Loane et al. (2000a) found that an initial dermatology consultation by cost $26.90 compared with $132.10 for an initial real-time consultation i.e. store-and-forward teledermatology was 20% of the cost of real-time teledermatology.

- The RCT in the UK by Loane et al. (2001a) found that the observed marginal cost of an initial real time teledermatology consultation was £52.85 for patients in urban areas and £59.93 for patients in rural areas. The observed marginal cost for the conventional consultation was £47.13 for patients in urban areas and £48.77 for patients in rural areas.

- The RCT undertaken in New Zealand by Loane et al. (2001b) found that the average cost of a teledermatology consultation was NZ$279.23 compared to NZ$283.79 for a face-to-face consultation, assuming an average distance to a local health centre of 12.6.km and 267 km to a specialist hospital. Most savings were for patients rather than health providers.

- The systematic review which included non randomised studies by Whitten et al. (2002) found that primary studies were inconsistent in their findings on the cost effectiveness of teledermatology and concluded that there is little published evidence to confirm whether or not telemedicine is a cost effective alternative to standard care.

- The RCT undertaken in the UK by Wootton et al. (2000) concluded that real time teledermatology was not cost effective compared with conventional dermatological outpatient care but that if the travelling distances were greater (78 km instead of 26 km) teledermatology would be a cost effective alternative to conventional care.

# EVIDENCE TABLE 4.5

## *In patients with suspected skin cancer, is teledermatology effective in terms of cost?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bergmo 2000) | To determine the cost differences between alternative methods of providing dermatology services to patients living in remote areas. | Retrospective case series.<br><br>Review of routinely collected data, patients referred to the routine real time teledermatology service. | 375 patient referred in 1998 to dermatology services either teledermatology or face-to-face.<br><br>**Norway** | Costs comparisons of teledermatology with 3 alternative methods of treatment - travel to nearest secondary care, locally employed dermatologist, and combination. | Teledermatology cost less, NKr 470,780, travel to nearest secondary care NKr 1,635,075, locally employed dermatologist NKr958,660, and combination NKr 880,530. | A cost study not an economic evaluation. Authors state effectiveness established in previous pilot. Distances involved 800km 12 hour drive Generalisability not addressed Cancer patients not included referred straight to hospital for face-to-face. | 3 |
| (Burgiss *et al.* 1997) | To assess the effect of store and forward teledermatology consultations on the cost of care for a given episode of illness. | Retrospective case series, cost study. | 87 patients, 119 visits, in a 17-month period 1995-1997.<br><br>Of these 3 SCC and 2 BCC (6%).<br><br>**US** | Comparison group not explicitly stated but presumed to be the costs incurred in primary care by same patients for 8 months prior to teledermatology consultation. | 7 teledermatology patients (8%) required face-to-face follow-up, 20 patients (23%) (52 visits) had follow-up teledermatology appointment. The average cost of care for the diagnosed dermatologic condition, for all patients during an average period of 8 months prior to teledermatology was $294, compared with $141 for the 6 months after diagnosis by teledermatology. | Cost comparison group choice obscure, and time period not equal. Costs included – medication, consultations, and diagnostic lab costs, no set-up, fixed, Treat with caution. Generalisability not addressed. | 3 |
| (Chan *et al.* 2000) | To test the | Case series, cost | 74 patients | Diagnostic | Authors cite diagnostic accuracy teledermatology to be 74.3%, | No details of referral | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | feasibility of establishing a teledermatology service for older people living in residential/nursing care homes. | study. | referred for specialist dermatological opinion, all patient experienced a video teledermatology consultation and were then seen face-to-face with the same dermatologist.<br><br>**Hong Kong** | accuracy and management. Comparison between real time teledermatology appointment and face-to-face appointment. All patients seen in person to establish diagnostic accuracy of the teledermatology system, then costs calculated. | uncertain diagnosis 8% (n=6) and different diagnoses 17.6% (n=13).<br>Cost per patient (HK$) teledermatology 57.7<br>face-to-face- patient travelling to consultant 322.8<br>Face-to-face - consultant travelling 445.9<br><br>Between 48 and 145 patients needed to be seen by teledermatology to offset maintenance costs of teledermatology system.<br>Exchange rate cited as £1=HK$12.6. | criteria or diagnosis. Effectiveness not established.<br>No statistical or sensitivity analysis conducted, no cost year.<br><br>Authors do not address generalisability. | |
| (Hailey *et al.* 2002) | To provide an update of a previous overview of the evidence of efficacy and cost effectiveness of telemedicine. | Systematic review of all telemedicine evaluations Explicit inclusion criteria provided. | 4 teledermatology studies included, 2 Loane papers NZ and NI, Chan and Bergmo overall 604 papers of which 46 met inclusion criteria 16 of which were economic evaluations.<br><br>**Canada** | Economic effect, patient outcomes. | Teledermatology indicated that there were cost disadvantages to healthcare providers, though not to patients, particularly those with longer journeys. | Explicit search strategy.<br>Good quality studies are still scarce and generalisability of most assessment findings may be limited. | 1 + |
| (Lamminen *et al.* 2000) | To establish how well videoconferencing works in clinical practice. | Case series:<br><br>Very small pilot study involving one remote health centre with 5 referring GPs, and 1 hospital based consultant | 25 patients, had been referred to teledermatology for diagnostic opinion (n=14), treatment opinion (n=18) and advice on referral speciality (n=3). | Diagnosis, and need for follow-up.<br><br>Cost (set-up and running costs). | Diagnoses were changed in 13 cases (52%). Two of the 25 patients had a confirmed diagnosis of skin cancer, 1 BCC and 1 SCC (8%).<br>Costs of teleconsultation – FM18,627, and face-to-face FM18,034.<br>No cost year stated, or exchange rate. Main economic benefits reduced travel. | A cost study: no measure of effectiveness was made. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | dermatologist. | **Finland** | | | | |
| (Loane *et al.* 2000a) | To evaluate the clinical efficacy and cost effectiveness of real-time and store-and-forward teledermatology.<br><br>Part of UK multi-centre trial, duplication of patients in Wootton and Oakley study. | Repeated measures, case series. | 96 of the 102, patients in the real time teledermatology arm of the RCT also had store and forward teleconsultation. Instant camera used, photo and referral letter posted to 2nd dermatologist fro opinion.<br><br>4 health centres, (2 rural 2 urban) and 2 hospitals dermatology departments.<br><br>**UK** | Comparison between diagnoses, management plan and associated costs, for both types of consultation. | Agreement between the video link diagnosis and the still image diagnosis was in 51% of cases. The same or similar management plan was recommended at both types of consultation in 44% of cases. Following the store-and-forward consultation the dermatologist recommended that 69% of patients required at least one hospital appointment compared with 45% of those patients seen in real-time. The net societal cost of the initial real-time consultation was $132.10 per patient compared with $26.90 per patient for the initial store-and-forward consultation. | Cost study, not economic analysis Effectiveness not established here for either method Store-and-forward least costly of the 2, but less clinically effective.<br>No opportunity to interact with patient in the store-and-forward limited the dermatologists ability to diagnose and manage the patient. | 3 |
| (Loane *et al.* 2001a) | Evaluation of the cost-effectiveness of real time teledermatology compared with conventional out-patient care in rural and urban areas. | RCT<br><br>Part of UK Multi-centre trial, possible overlap of included patients. | 274 Patients, 126 real time teledermatology and 148 OPD face-to-face. One district general hospital, 1 urban health centre and 1 rural health centre.<br><br>**UK** | Patient outcomes and societal costs of initial teledermatology compared with initial face-to-face consultation, for rural and urban patients. | Clinical outcomes similar in both groups, Almost half managed in primary care after 1 consultation with dermatologist. Observed marginal cost of initial real time teledermatology consultation was £52.85 in urban and £59.93 for rural patients. The observed marginal cost for the conventional consultation for was £47.13 for urban and £48.77 for rural patients. | No diagnosis stated; population was "patients with dermatological conditions requiring a specialist referral".<br><br>Provider perspective: total cost of telemedicine consultations higher in both urban and rural areas than conventional face-to-face.<br><br>Patients' | 1 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | perspective: costs lower for telemedicine time and travel.<br>Economic evaluation conducted including sensitivity analysis. | |
| (Loane *et al.* 2001b) | Economic evaluation – cost minimisation to compare the societal costs of real time teledermatology with conventional face-to-face consultations. | RCT<br><br>1 specialist hospital and 2 rural health centres. Real time teledermatology. | 203 patients were referred for randomisation to real time teledermatology (n=109) or conventional face-to-face appointment (n=94).<br>Follow-up appointment requires for 14 in teledermatology and 12 in face-to-face.<br>Duration 10 months.<br><br>**New Zealand.** | Comprehensive costs included patients costs elicited by questionnaire, included fixed, direct indirect costs, time and follow-up appointment. | Average costs: teledermatology cost NZ$279.23 and face-to-face diagnosis NZ$283.79, assuming average travel distance to local health centre 12.6.km and 267 km to specialist hospital.<br>Marginal analysis – cost of seeing additional teledermatology patients $135 and $284 for face-to-face.<br>Most savings were for patients rather than providers. | No details of diagnosis, referral as above.<br>Sensitivity analysis conducted, various scenarios assuming 10% decrease and increase in referral as well as no change. | 1 |
| (Whitten *et al.* 2002) | To systematically review cost benefits studies of telemedicine. | Systematic review.<br><br>Inclusion criteria – extended beyond RCTs as too few, to include original report on telemedicine examining cost effectiveness of healthcare delivery. English only | Patients for whom teledermatology was used.<br><br>612 articles produced 55 with cost data but only 24 fulfilled inclusion criteria. Authors to not break down telemedicine into different applications, e.g. .teledermatology | Scientific quality of reports using an established instrument for economic analyses. | Most reports from US and Norway<br>20 36% conclude that telemedicine saves money, 11 (20%) saves time and money, 9 (16%) only cost effective if a certain threshold of patient throughput achieved, and a 7 (13%) that further work is needed to determine cost effectiveness, 4(7%) other and 4 studies (7%) say telemedicine does not save money. | Explicit search strategy.<br>General – no separation of telemedicine into dermatology, and other applications.<br>Authors conclusions – there is little published evidence to confirm whether or not telemedicine is a cost effective alternative to standard care. | 1 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | Exclusion – Duplicates Telemedicine used mainly for education or admin Hypothetical costs analyses, or modelling without associated clinical trial Economic analysis without substantiating claimed resource use. | nor does the paper give full references of all included studies.<br><br>**US** | | | | |
| (Wootton *et al.* 2000) | To assess the cost effectiveness of real time teledermatology with conventional face-to-face consultations with a dermatologist.<br><br>Part of UK multi-centre trial, possible overlap of included patients. | RCT<br><br>2 hospitals and 4 health centres, (2 rural 2 urban). | 204 patients, N. Ireland. 102 randomised to teledermatology, all real time with 96 having additional store-and-forward images, and 102 to conventional out-patient visit (face-to-face). No loss to follow-up12 month period 130 patients completed economic questions.<br><br>**UK** | Intention to treat used for effectiveness analysis. Reported clinical outcome of initial consultation, primary care and outpatient re-attendance data, and cost benefit analysis of both methods of delivering care. | Similar clinical outcomes between groups. Teledermatology patients 54% (n=55) managed in primary care. 46% (n=47) needed subsequent face-to-face appointment compared with 45% (n=46) needing follow-up following face-to-face appointment.<br><br>Telemedicine costs £201.88 and face-to-face £48.72. Cost saving in reduced referrals + training costs £69.78. GP estimated drop in referrals of average of 20%. Overall societal cost of teledermatology £132.10.<br><br>If round trip to hospital 78km not 26km the costs would have been equal.<br><br>The net societal cost of the initial consultation was £132.10 per patient for teledermatology and £48.73 for conventional consultation. Sensitivity analysis revealed that if each health centre had allocated one morning session a week to teledermatology and the average round trip to hospital had been 78 km instead of 26 km, the costs of the two methods of care would have been equal.<br><br>Authors conclude that real time teledermatology was clinically feasible but not cost effective compared with conventional dermatological outpatient care. However, if the equipment were purchased at current prices and the travelling distances greater, teledermatology would be a cost effective alternative to conventional care. | No details of patients referral criteria beyond “patients with dermatological conditions requiring a specialist referral”. No details of diagnosis. Real time teledermatology clinically feasible, but not cost effective compared with conventional care. With decreased equipment costs and greater travel distance then would be cost effective. Well conducted RCT, blind randomisation procedure, power calculation, Sensitivity analysis, | 1 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | too short-term for cost discounting. | |

# Staging of skin cancer

## Surgical staging of skin cancer

### Sentinel node biopsy

#### The questions

*How effective is sentinel lymph node biopsy (SLNB) as a prognostic indicator for patients with primary melanoma?*

*What is the impact of SLNB on survival for patients with primary melanoma?*

*What is the impact of SLNB on quality of life for patients with primary melanoma?*

#### The nature of the evidence

At the time of conducting this evidence review, further survival data for patients with melanoma who undergo SLNB are anticipated from the Multi centre Selective Lymphadenectomy Trial (MSLT), undertaken by Morton et al. Although some preliminary data have been presented at conferences, no published report is yet available to inform this guidance.

Eighteen studies were identified, as follows:

- One systematic review of good quality
- Eleven observational studies, six of good quality, four of fair quality and one of poor quality
- Two clinical guidelines of good quality
- Four expert reviews of fair quality

Six studies originate from the UK, five are from the US and two studies are from Australia. The remaining five studies are from Western Europe. Applicability to the UK is limited.

All eighteen studies are of patients with primary melanoma, and although disease stages vary, primary tumour thicknesses are greater than 1mm in the majority of studies. One study is of patients with melanoma of the head or neck.

**Summary of the supporting evidence for the recommendations**

**SLNB as a prognostic and staging indicator**

**Evidence from one systematic review and observational studies suggests that the status of the sentinel lymph node is a prognostic factor, as are characteristics of the primary tumour, and may be used to stage the progression of disease in patients with melanoma and identify patients for adjuvant therapy. Some expert opinion questions the prognostic significance of very small (<1mm) metastatic deposits in the sentinel node, whereas larger metastatic sentinel node tumours are generally accepted as being prognostically equivalent to clinically detectable nodal disease. Estimates of rates of tumour positive sentinel nodes in observational studies range from 14.6% to 20.7% and this proportion increases with increasing Breslow thickness. Estimates of the false negative rate of SLNB in observational studies range from 2.6% to 9.1%. False negative SLNB results are more likely to arise from thinner primary tumours. Systematic review evidence suggests that SLNB should be considered for patients with melanoma on an individual basis, based upon Breslow thickness and other prognostic factors, but is appropriate for patients with primary melanoma tumours with Breslow thickness between 1.51 and 4.0 mm. Observational study evidence suggests that interval nodes may also be of value in staging melanoma progression.**

**Evidence based clinical guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that SLNB should be considered as a staging technique in patients with a primary melanoma ≥ 1mm thick or a primary melanoma < 1mm thick of Clark level 4, whereas clinical guidelines produced by the British Association**

**of Dermatologists recommend that the procedure should only be used in specialist centres within clinical trials.**

- The case series study by Caggiati et al. (2000) found the overall incidence of positive sentinel nodes in melanoma patients to be 14.6%. Incidence correlated with thickness of primary lesion (0.75-1.5 mm: 7.3%; 1.5-3 mm: 14.9%; 3-4 mm: 30.5%). Metastasis in non-sentinel nodes was found only with primary tumour thickness exceeding 2 mm. The authors concluded that SLNB is important for staging disease and identifying patients for adjuvant therapy.

- The prospective, observational study by Estourgie et al. (2003) found the false negative rate of SLNB at median 72 month follow-up to be 9.1% with a negative predictive value of 96.5%. Recurrence occurred in 16% of patients with negative SLNB results and in 47% of patients with positive SLNB results.

- The expert review (awaiting publication) by Giblin, Hayes, and Thomas (2005) reported that in patients with melanoma who undergo SLNB, a proportion of melanoma deposits found in sentinel nodes are less than 1mm in diameter and concluded that the significance of micrometastatic deposits in the sentinel node is uncertain, and that such deposits may not be prognostically similar to overt nodal metastases.

- The expert review by Johnson et al. (2004) concluded that routine tests have little efficacy and are not cost-efficient for detecting occult disease in asymptomatic patients with localised melanoma and that the only staging test that has relatively high sensitivity and specificity and provides tissue diagnosis is SLNB.

- The systematic review by Lens et al. (2002b) found the proportion of tumour positive sentinel nodes based upon 12 studies to be 17.8 [95% CI 16.7 to 19.0] and this proportion correlated strongly with Breslow thickness. The authors recommended that SLNB is inappropriate for

tumours with Breslow thickness < 1mm, and for Breslow 1.0 – 1.5 mm SLNB should be considered on an individual basis in the light of other prognostic factors and possible adjunctive therapy, and for Breslow thickness between 1.51 and 4.0 mm, SLNB is appropriate. The authors reported that the value of SLNB for Breslow thickness > 4.0 mm is questionable due to the risk of haematogenous spread.

- The large, retrospective study by Morton et al. (2003) found that sentinel node metastases were found in 20.7% of patients who underwent SLNB with known Breslow thickness, with greater numbers of positive sentinel nodes identified for thicker primary tumours. The false negative rate of SLNB was 2.6% and these missed positive nodes were found to arise from tumours ≤ 2.0mm in thickness.

- Evidence based guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists recommend the use of SLNB as a staging procedure in patients with stage II melanoma in specialist centres in clinical trials but unless evidence emerges for a role in determining outcome it should not be routine.

- Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that SLNB should be considered as a staging technique in patients with a primary melanoma ≥ 1mm thick or a primary melanoma < 1mm thick of Clark level 4.

- The prospective, observational study by Statius Muller et al. (2001) found sentinel node status to be a significant prognostic factor for patients with melanoma, as were Breslow thickness, ulceration and lymphatic invasion.

- The large, retrospective case series study of patients with melanoma 1mm thick or greater by Uren et al. (2000), found that micrometastases were detected in 14% of interval nodes examined by SLNB. The incidence of metastasis was found to be similar between interval sentinel nodes and sentinel nodes within recognised node fields. The

authors recommended that interval nodes should be excised along with sentinel nodes, since they can be the only nodes to exhibit metastasis.

**SLNB and survival**

**No randomised controlled, trials have been published reporting on survival following SLNB in patients with melanoma. There is evidence from observational studies that the status of the sentinel node significantly predicts disease free survival, with OR for disease free survival at 3 years based on negative sentinel node status estimated as 5.2 [95% CI 2.0 to 13.7] by Statius Muller et al. (2001). Observational study evidence is suggestive of a survival advantage (in terms of overall survival and disease free survival) arising from early, complete lymph node dissection following a positive SLNB result, over delayed, complete lymph node dissection performed at the onset of clinically evident regional lymph node involvement.**

- The observational study by Cherpelis et al. (2001) found that in patients with thick melanoma tumours disease-free survival (3-year) was significantly greater for patients with negative sentinel nodes than for patients with positive sentinel lymph nodes, but there was no significant difference in overall survival. Tumour ulceration was the only histological factor found to be predictive of outcome.

- The prospective, observational study by Estourgie et al. (2003) estimated disease free survival for patients with disease negative and disease positive sentinel node status, as 85% and 63% respectively after 3 years and 80% and 53% respectively after 5 years. Overall survival for patients with disease negative and disease positive sentinel node status was 92% and 79% respectively after 3 years and 89% and 64% respectively after 5 years.

- The unpublished expert review by Giblin, Hayes, and Thomas (2005) cited the above study by Morton et al. (2003), questioning the assumption that patients with positive SLNB results are prognostically

equivalent to patients who develop overt nodal metastases following wide excision alone.

- The retrospective, case series study by Kretschmer et al. (2005) found that overall survival at 5 years differed significantly between patients with negative SLNB result (90.1%), positive SLNB result (54.4%) and patients who underwent delayed lymph node dissection (37.4%). Disease free survival differed significantly between patients with negative SLNB result (77.7%), patients with positive SLNB result (38.6%) and patients who underwent delayed lymph node dissection (11.6%).

- The large, retrospective study with paired analysis of 287 patient pairs by Morton et al. (2003) demonstrated a survival advantage at 5, 10 and 15 years of early regional lymph node dissection after positive SLNB result, over delayed regional lymph node dissection after wide excision of primary tumour alone.

- The prospective, observational study by Statius Muller et al. (2001) estimated the odds ratio for 3 year disease free survival for patients with negative sentinel lymph node status to be 5.2 [95% CI 2.0-13.7], for patients with tumours of Breslow thickness 1.01-2.0 mm to be 21.9 [95% CI 2.6-183.3], for patients with ulceration absent 2.5 [95% CI 1.0-6.5] and for patients with lymphatic invasion absent 5.7 [95% CI 1.4-22.1]. The authors concluded that sentinel node status, Breslow thickness, lymphatic invasion, ulceration were predictive of 3 year survival.

**SLNB and quality of life**

**Evidence from observational studies suggests that whilst surgical complications can arise from SLNB, the procedure is less invasive than a regional lymphadenectomy and may be undertaken in the head and neck region. The same level of evidence suggests that short term psychosocial benefits may arise from sentinel lymph node biopsy independent of the result itself.**

- The prospective, observational study by Estourgie et al. (2003) found that 48% of patients who underwent regional lymph node clearance after positive SLNB experienced complications due to surgery including seroma, oedema, wound or limb infection, necrosis, dehiscence, haematoma and transient neuropraxia. Late complications were seen in 18% of patients who underwent SLNB without further surgery including minor oedema, infection, seroma, transient sensibility impairment and transient neuropraxia.

- The qualitative survey by Rayatt et al. (2002) concluded that most melanoma patients derive at least short term psychosocial benefits from SLNB independent of the result itself, although they remained concerned about their disease status.

- The case series study by Schmalbach et al. (2003) investigated the reliability and surgical safety of SLNB in staging melanoma of the head and neck and concluded that SLNB can be reliably and safely performed in the neck and parotid regions. The authors stressed the importance of multidisciplinary cooperation to ensure this.

**Locoregional recurrence**

**There is some evidence from observational studies and one expert review to suggest increased locoregional recurrence of melanoma, in patients who have undergone SLNB, compared to patients who receive delayed regional lymphadenectomy after detection of clinically palpable lymph nodes. Locoregional recurrence is more likely where SLNB identifies sentinel node disease than where the SLNB result is negative. However, a single observational study made a distinction between locoregional recurrence as a first recurrence and locoregional recurrence that may follow recurrences in lymph nodes or distal recurrences. This study found that whilst 5 year locoregional recurrence as first recurrence was higher in patients with positive SLNB results than in patients who undergo delayed lymphadenectomy, there was no**

**significant difference in incidence of recurrence overall, between these two patient groups.**

- The prospective, observational study by Estourgie et al. (2003) found that in-transit recurrence occurred in 7% of patients with negative SLNB results and 23% of patients with positive SLNB results.

- The case series study by Estourgie, Nieweg, and Kroon (2004) found that in patients with melanoma who underwent SLNB, the incidence of in-transit metastases was 23% in patients with a disease positive sentinel node compared to 8% in patients who did not undergo SLNB and subsequently developed palpable nodes.

- The retrospective case series study by Kretschmer et al. (2005) found the rate of locoregional recurrence *as a first recurrence* at 5 years in patients with melanoma who receive a disease negative SLNB result to be 6.9%, for patients with a disease positive SLNB result this value was 27.3%, and in patients who received delayed lymph node dissection at the onset of clinically detectable lymph node disease this value was 17.6%. However there was no significant difference in the 5 year rate of *overall* locoregional recurrence between patients with positive SLNB result (33.7%) and those with delayed lymph node dissection (33.3%).

- The expert review by Pawlik et al. (2005) concluded that the occurrence of in-transit disease in melanoma depends upon tumour biology and not whether SLNB has been performed. The review cited a study in press which reported no significant difference in rates of in-transit recurrence between patients treated by wide excision plus SLNB compared to those treated with wide excision alone, where tumour prognostic factors were similar between groups.

- The expert review by Thomas and Clark (2004) found that primary studies reported rates of local / in-transit recurrence in patients with melanoma who receive wide excision alone with range 2.5 – 6.3%. The rate of local / in-transit recurrence after SLNB was 9.0% (with or

without selective lymphadenectomy) i.e. 5.7% following SLNB alone, and 20.9% after SLNB plus selective lymphadenectomy in patients with disease positive sentinel nodes.

- The retrospective case series study by Van Poll et al. (2005) measured rates of in-transit recurrence in 2018 patients with primary melanomas ≥1.0 mm thick. There were no significant differences in rates of in-transit recurrence, or in rates of in-transit recurrence as the first site of recurrent disease, between patients treated with wide local excision only, wide local excision plus SLNB, and wide local excision plus elective lymph node dissection.

# EVIDENCE TABLE 4.6

***What is the impact of sentinel node biopsy on quality of life for patients with primary melanoma?***

***How effective is sentinel node biopsy as a prognostic indicator for patients with primary melanoma?***

***What is the impact of sentinel node biopsy on survival for patients with primary melanoma?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Caggiati *et al.* 2000) | To report on a case series of patients, focussing on detection rates of the sentinel node, relationship between primary tumour thickness and sentinel node status and technical aspects of the procedure. | Retrospective case series. | 259 patients with primary melanoma .075 to 4.0 mm thickness treated by excision and without clinically detectable nodal involvement.<br><br>**Italy** | Detection rates with and without gamma probe, comparison of incidence of metastasis in sentinel versus non sentinel nodes, according to clinical stage of disease. | The overall detection rate of SLNs was 96%. The overall incidence of positive sentinel nodes was 14.6%. Incidence correlated with thickness of primary lesion (0.75-1.5 mm: 7.3%; 1.5-3 mm: 14.9%; 3-4 mm: 30.5%). Metastasis in other non-sentinel nodes was found only with primary tumour thickness exceeding 2 mm. A specific learning phase (>30 patients) is recommended for reliable results. An improvement in survival rates by sentinel node biopsy has not yet been demonstrated, but this more accurate N-staging procedure offers clear advantages in terms of the patient's quality of life, prognosis, and indication for adjuvant therapy. Authors conclude that SLNB is important for staging disease and identifying patients for adjuvant therapy. | All patients with positive SLNs underwent radical lymphadenectomy as did those in whom no sentinel node could be identified. Authors note that SLNB is a procedure requiring a multidisciplinary approach (surgery, nuclear medicine, and pathology). General anaesthesia was required in 25% of patients where a gamma probe was used. Authors not reasons for failure of SLNB as surgical errors, anatomic anomalies, inaccurate lymphoscintigraphy and pathological false negatives. | 3 |
| (Cherpelis *et al.* 2001) | To evaluate the influence of sentinel lymph node | Retrospective analysis of patient | 201 patients (130 male, 71 female) | Histological variables, sentinel | The mean overall and disease-free survival rates were 78% and 66%, | Patients with positive sentinel nodes offered complete node | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | histology and other microscopic parameters on survival of patients with thick melanomas. | record database. All 201 subjects included underwent wide local excision and SLNB. | with thick melanoma tumours i.e. 3 mm or greater. Mean age 60.1 years.<br><br>**US** | node status, survival. | respectively. There was a statistically significant difference in disease-free survival (3-year) between sentinel node positive and sentinel node negative patients (37% vs. 73%, respectively; P =.02). The overall survival (3-year) for the sentinel node positive patients was less than the sentinel node negative patients (70% vs. 82%), but it was not statistically significant (P =.08). The disease-free survival for patients with ulcerated lesions was less than for nonulcerated lesions (77% vs. 93%, P =.05). None of the other histologic parameters studied, including Breslow thickness, Clark level, mitotic rate, or regression, had an influence on the overall or disease-free survival in this group of patients with thick tumours. | dissection and adjuvant therapy. The authors conclude that SLNB appears to be justified for prognostic purposes in patients with thick melanomas. None of the histologic features of the primary tumour were helpful in predicting outcome, except for ulceration. | |
| (Estourgie *et al.* 2003) | To prospectively evaluate the benefits and untoward sequelae of SLNB at a single centre from 1993. | 250 patients with melanoma. | 250 patients with melanoma. Mean Breslow thickness 2.7 mm and Clark level II to V. Ulceration confirmed in 32% of cases.<br><br>**Holland** | Post operative and late complications, follow-up, recurrence, overall and disease free survival analysed. | 60 (24%) patients had positive sentinel nodes at pathology evaluation, all of whom underwent completion lymphadenectomy and metastasis was found in 12% of these patients and only when Breslow was 1.1mm or less. SLNB false negative rate at median 72 month follow-up was 6/66 (9.1%) i.e. NPV 96.5%. Recurrence occurred in 31 (16%) of 190 SLNB negative patients and in 28 (47%) of 60 SLNB positive patients. In-transit recurrence occurred in 7% of sentinel node negative patients and 23% of sentinel node positive patients. Disease free survival for patients with disease negative and positive SLNB was 85% and 63% respectively after 3 years and 80% and 53% respectively after 5 years ($p < 0.001$). Overall survival for patients with disease negative and positive SLNB was 92% and 79% respectively after 3 years and 89% and 64% respectively after 5 years ($p < 0.001$). | Baseline characteristics reported. Median follow-up 72 months, range 12.3-104.4 months. SLNB and wide excision performed during same procedure. Mean 2.3 sentinel nodes and mean 4 non sentinel nodes collected per patient. 23 (9.2%) of 250 patients experienced postoperative complications. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Estourgie *et al.* 2004) | To compare the incidence of in-transit metastases in 61 patients who had lymph node dissection because of a tumour-positive sentinel node with that in 60 patients who had palpable nodal metastases dissected. | Case series with comparison between two patient groups: group 1: 61 patients with positive sentinel nodes identified by SLNB, studied prospectively. Group 2: 60 patients with palpable lymph node disease (initial stage I-II disease) studied retrospectively. | Patients with melanoma metastatic to lymph nodes (Primary melanoma tumours 1mm thickness or more, or thinner if the Clark level was IV or V).<br><br>**Holland** | Incidence of in-transit metastases. | The incidence of in-transit metastases was 23 per cent in patients with a positive sentinel node and 8 per cent in those with palpable nodes (P = 0.027, Chi square). In logistic regression, the difference in in-transit recurrence remained significant (p = 0.022), where no other patient or tumour characteristics were of significant prognostic value. Authors concluded that sentinel node biopsy was associated with a higher risk of in-transit metastases. | Patient groups differed significantly for Breslow thickness and ulceration in primary tumour.<br><br>Study does not report whether log regression was multiple, or repeated single. | 3 - |
| (Giblin *et al.* 2005) | To question the assumption, often made in the literature, that sentinel node positive patients are prognostically equivalent to patients who develop overt nodal metastases. | Expert review (submitted as expert position paper, with publication anticipated). | Patients with melanoma.<br><br>**UK** | Authors cite findings of selected primary studies and develop arguments. | Authors argue that:<br>• The paper by Morton et al. (2003, see below) assumes that patients with positive sentinel nodes are equivalent to those with overt nodal disease<br>• Two thirds of melanoma deposits found in sentinel nodes are less than 1mm in diameter and the size of metastatic deposits and tumour burden influence the potential for further spread of disease.<br>• Some micrometastases detected by SLNB may be misclassified non malignant cell colonies<br>• Larger (> 1mm) metastatic deposits in the sentinel node carry an equivalent prognosis to that seen following delayed lymph node dissection (to treat overt nodal disease).<br>• Some micrometastases lack the potential for further spread of disease and are contained by the immune system<br>• Authors conclude that the significance of micrometastatic deposits in the sentinel nose is uncertain, and that | The MSLT-1 sentinel lymph node biopsy trial results by Morton et al. are awaited. | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | such deposits may not be prognostically similar to overt nodal metastases. | | |
| (Johnson *et al.* 2004) | To clarify and update workup and follow-up strategies based on fundamental principles and current data and to discuss new and current concepts regarding sentinel lymph node biopsy (SLNB), particularly in relation to the staging workup. | Review/discussion. | Studies pertaining to staging workup, SLNB and follow-up tests.<br><br>**US** | Poorly defined: findings of primary studies cited. | Routine tests have marginal to no efficacy and are not cost-efficient for detecting occult disease in asymptomatic patients with localised melanoma. The only staging test that has relatively high sensitivity and specificity and provides tissue diagnosis is SLNB. | Apparent systematic review but insufficient details of methods provided. | 4 |
| (Kretschmer *et al.* 2005) | To evaluate recurrence of melanoma following SLNB compared with that following delayed lymph node dissection in patients with clinically palpable lymph nodes. | Retrospective case series analysis using Kaplan Meier plots with recurrence as end points. | 443 consecutive patients with melanoma who met the criteria for SLNB at the time of diagnosis: 244 patients who underwent SLNB and 199 controls who received delayed regional lymphadenectomy.<br><br>**Germany** | locoregional cutaneous metastases, both as first recurrence and overall. Overall survival and disease free survival. | For sentinel node *negative* patients ( who were diagnosed with primary melanoma > 1mm thick) the 5 year probability of developing a locoregional cutaneous metastasis as a *first recurrence* was 6.9% and this probability was 17.6% in the delayed lymph node dissection group (p = 0.028). Comparing patients with positive nodes in each group, the probability of developing a locoregional recurrence as a *first recurrence* was higher in patients in the SLNB positive group (27.3%) vs. 17.6% in the delayed lymph node dissection group (p = 0.03). The 5 year *overall* probability of developing a locoregional recurrence (i.e. including recurrences other than first recurrence) did not differ significantly between the SLNB positive (33.7%) and delayed axillary dissection (33.3%) groups (p = 0.38). Overall survival at 5 years differed significantly between SLNB negative (90.1%), SLNB positive (54.4%) and delayed lymph node dissection (37.4%) groups. Disease free survival differed significantly between SLNB negative (77.7%), SLNB positive (38.6%) and delayed lymph node | Includes loco-regional recurrence that were not first recurrences, but excludes recurrences that were excised along with the primary tumour and also those arising in the scar of previous lymphadenectomy. Longer follow-up observed in control group to SLNB group. Confounding factors analysed between positive SLNB and delayed dissection groups: only Breslow thickness significantly predicted locoregional recurrence. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | dissection (11.6%) groups. The median interval from primary tumour excision and nodal recurrence was 12 months for patients with delayed lymph node dissection. This was compared with patients with positive SLNB, in whom the interval from excision of primary tumour to first nodal or (mostly) distant recurrence was 47.5 months ($p < 0.00001$). Authors conclude that SLNB followed by regional lymphadenectomy increases the recurrence free interval and the overall locoregional recurrence risk (i.e. including recurrences that are not first recurrences) is not increased following SLNB. | | |
| (Lens *et al.* 2002c) | To determine the degree to which Breslow thickness is predictive of sentinel node metastasis and whether patients may be selected for SLNB accordingly. | Systematic review of 12 studies with a sum population of 4218 subjects. | Patients with cutaneous melanoma AJCC stage I and II.<br><br>**UK** | SLNB positive rates compared with Breslow thickness. | The proportion of tumour positive sentinel nodes was 17.8 [95% CI 16.7 to 19.0]. and correlated strongly with Breslow thickness ($p < 0.001$). The incidence of micrometastases in sentinel nodes correlated directly with Breslow tumour thickness; it was 1.0% for lesions of less than or equal to 0.75 mm, 8.3% for 0.76-1.50 mm, 22.7% for 1.51-4.0 mm and 35.5% for more than 4.0 mm. Authors conclude: SLNB is inappropriate for tumours with Breslow thickness < 1mm. For Breslow 1.0 – 1.5 mm SLNB should be considered on an individual basis in the light of other prognostic factors and possible adjunctive therapy. For Breslow thickness between 1.51 and 4.0 mm, SLNB is appropriate. The value of SLNB for Breslow thickness > 4.0 mm is questionable due to the risk of haematogenous spread. Breslow thickness is predictive of sentinel node metastasis, however SLNB is not the standard of care. | English language only studies included. No grading of study quality or measure of heterogeneity included. | 1 + |
| (Morton *et al.* 2003) | To determine the diagnostic and | Large retrospective analysis of a case | Patients with melanoma of varied | Overall survival. | Sentinel node metastases were found in 20.7% of patients who underwent SLNB | SLNB in this study was preceded by lymphatic | 3 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | therapeutic utility of SLNB when preceded by lymphatic mapping, to investigate carbon dye for mapping the microanatomy of flow within the sentinel node and to determine the prognostic accuracy of molecular assessment of the sentinel node. | series of 1599 patients who underwent SLNB and 4590 that underwent wide excision alone. Study compares incidence of sub clinically positive sentinel nodes detected by SLNB, incidence of clinical nodal recurrence following negative SLNB result and incidence of clinical nodal recurrence following wide excision alone. | Breslow thickness and Clark level.<br><br>**US** | Study also evaluates 2 novel techniques:<br><br>i) Mapping specific areas of the sentinel node (with carbon dye) where tumour cells are thought to enter in order to avoid falsely negative SLNB result.<br><br>ii) Molecular analysis of paraffin embedded sections of sentinel node tissue. | with known Breslow thickness: 7.3%, 19.7%, 33.2%, and 39.7% for tumours ≤1.0, 1.01-2.0, 2.01-4.0 and >4.0mm respectively, corresponding with clinical nodal recurrence rates of 12.0%, 32.0%, 34.4% and 30.1% respectively for patients who underwent wide excision alone. SLNB by immunohistology had a false negative rate of 2.6% and these missed positive nodes were found to arise from tumours ≤ 2.0mm, based upon expected numbers from patients who develop clinically palpable nodes following wide excision alone. The carbon dye and molecular staging techniques were found to enhance the diagnostic and prognostic accuracy over the standard techniques. Paired analysis of 287 patient pairs showed a survival advantage of early completion lymphadenectomy after positive SLNB over delayed completion lymphadenectomy after wide excision alone: the respective 5, 10 and 15 year survivals were 73%, 69% and 69% versus 51%, 37% and 32% ($p \leq 0.001$). 69% of patients were therefore potentially curable by early resection. Since 32% of patients with clinically enlarged lymph nodes after wide excision were alive at 15 years, delayed completion lymphadenectomy may also be curative for some patients. Authors conclude that the risk of metastasis to the sentinel node and non sentinel nodes is directly proportional to primary tumour thickness: primary tumours < 1mm have low incidence of sentinel node metastases; tumours of ≥ 1.0 mm are likely to have sentinel node metastases; tumours 1.01-2.0 mm thick are likely to have only sentinel node | mapping with carbon dye. | |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | metastases and tumours of 2.01 or more are likely to have regional nodal or distant metastases. The authors conclude that this study supports the incubator hypothesis of disease progression, where disease exhibits a latent period of growth confined to the sentinel node. | | |
| (Pawlik *et al.* 2005) | To present evidence that the risk of in-transit melanoma metastasis is not increased by SLNB. | Expert review with authors' comments. | Patients with melanoma.<br><br>**Undertaken in the US** | Author draws conclusions from cited studies. | Authors cite evidence from studies which stands against the hypothesis that SLNB and/or lymph node clearance leads to increased rates of in-transit metastases, on the following points:<br>• Studies of SLNB have recruited patients with unfavourable tumour characteristics and sentinel node positive patients have predictably higher recurrence rates at all sites.<br>• A recent case series study in press found no significant difference in the rate of in-transit recurrence between patients treated with wide excision alone versus patients treated with wide excision plus SLNB. In this study tumour prognostic factors were similar between groups.<br>• Waiting for clinical nodal disease to develop may cause lymphatic obstruction.<br>• Studies have found that patients with occult node-positive disease treated by SLNB have a survival advantage compared to those treated with delayed lymph node clearance. | 25 references provided, but no evidence provided of a systematic literature search. | 4 |
| (Rayatt *et al.* 2002) | To investigate whether SLNB brings psychosocial benefit to patients who undergo the procedure for cutaneous melanoma. | Qualitative, retrospective survey of 98 patients who have undergone SLNB for melanoma, using interview | 98 patients with melanoma who underwent SLNB.<br><br>**UK** | Parameters measured covered patients' reported experiences including preoperative and postoperative | Patients reported concern with waiting time for the procedure (43%) and for the results of histology (85%). 85% thought the procedure provided peace of mind i.e. 68% of positive sentinel node patients and 90% of those with negative nodes. Most patients felt well looked | Questionnaire piloted prior to study initiation. 110 questionnaires distributed, 98 returned. Non responders contacted by telephone. Mean age 47 years with equal gender distribution. Replies | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | before and after the procedure. | | concerns and, time dependent trends evaluated by length of follow-up. | after (87%) or reassured the disease had not spread (72%) although reassurance declined with increasing follow-up (p = 0.02). 52% of patients felt there was no specific disadvantage from the procedure whereas 15% felt the major disadvantage was seroma formation, wound infection or pain. The authors conclude that most melanoma patients derive at least short term psychosocial benefits from SLNB independent of the result itself, although they remained concerned about their disease status. | received from all 19 patients with no complications (100%) and from 32/34 of those with documented complications (94%). No significant difference in non responders. | |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | Sentinel node biopsy can be used for staging in stage II melanoma in specialist centres in clinical trials but unless evidence emerges for a role in determining outcome it should not be routine. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Schmalbach *et al.* 2003) | To investigate the reliability of SLNB in staging melanoma of the head and neck and also the surgical safety of the procedure in the neck and parotid regions. | Retrospective analysis of a case series treated at a single centre. | 80 patients with melanoma of the head and neck; mean Breslow thickness 2.35 mm (range 0.7-7.0 mm).<br><br>**US** | % of positive sentinel nodes, false negative rate of SLNB, surgical complications. | Mean number of nodes identified per patient was 2.18 (range 1-7) nodes, 74% in neck basins and 26% in the parotid bed. 14 patients (17.5%) had positive sentinel nodes and 66 (82.5%) were sentinel node negative. Node negative patients were followed up with median 25 months (range 12-43 months). 8 (12%) of these developed recurrent disease with a false negative rate of 4.5%. One patient required superficial parotidectomy due to deep location of the sentinel node and a second had the SLNB aborted due to bleeding, but there was minimal morbidity associated with the procedure. The authors conclude that SLNB can be reliably and safely performed in the neck and parotid regions and stress the importance of | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | multidisciplinary cooperation to ensure this. | | |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Recommendations for practice. | SLNB should be considered as a staging technique in patients with a primary melanoma ≥ 1mm thick or a primary melanoma < 1mm thick of Clark level 4. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |
| (Statius Muller *et al.* 2001) | To investigate whether sentinel lymph node status is predictive of the proportion of patients remaining disease free at three years follow-up, compared with other prognostic factors. | Prospective prognosis study based upon a series of 263 patients. | Patients with melanoma AJCC stage I and II who undergo SLNB.<br><br>**Holland** | Disease free survival is measured. SLNB status and other prognostic factors analysed. | Sentinel node had metastatic deposits in 52 (20%) of patients. 49 patients underwent completion lymphadenectomy and three patients refused completion lymphadenectomy. Sentinel node was found by histology to be disease negative in 207 (79%) of patients. Subsequent follow-up found that SLNB had false negative rate 0f 4/56 (7%) and failure rate 4/263 (1.5%). Sentinel node status correlated with Breslow thickness from 8% disease positive sentinel nodes for 0.5-1.0 mm thickness to 63% for >4.0 mm. Three year disease free survival for patients with disease negative was 95% versus 79% for node positive patients. 5 year disease free survival was 91% and 49% respectively. These results were statistically significant. OR for survival at 3 years was 5.2 [2.0 to 13.7] according to sentinel node status. In addition, Breslow thickness, ulceration, lymphatic invasion and age (40-50 years) were significantly important prognostic factors. | 100% follow-up achieved with median 48 months, range 36-84 months. Sentinel node not removed in 4 (1.5%) patients due to surgical difficulty. Lymphoscintigraphy, blue dye and gamma probe used. In general, further nodes removed if showing > 10% radioactivity of sentinel node. | 3 + |
| (Thomas & Clark 2004) | To determine whether SLNB for melanoma | Expert review of studies of | Numerous populations of | Incidence of local / in-transit | The rate of local / in-transit recurrence after wide excision alone had range 2.5 | Literature review undertaken to identify studies reporting | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | alters the recurrence of local / in-transit metastases, particularly when followed by selective lymphadenectomy. | recurrence of melanoma following SLNB with or without selective lymphadenectomy. | patients with melanoma in primary studies, including those who underwent wide excision alone as first procedure, SLNB alone or SLNB plus selective lymphadenectomy.<br><br>**UK** | recurrence cited from primary studies. | – 6.3% based on three studies of patients with tumour thickness with respective range1.0 – 3.1 mm. The rate of local / in-transit recurrence after SLNB overall was 9.0% i.e. 5.7% following SLNB alone, and 20.9% after SLNB plus selective lymphadenectomy in patients with disease positive sentinel nodes. The authors conclude that there is an iatrogenic risk of local / in-transit recurrence arising from SLNB, with a fourfold incidence to that expected. | recurrence following SLNB, but details of search strategy and selection criteria not fully reported. Local and in-transit recurrence data were summed from each primary study, since they are both thought to arise from lymphatic dissemination. | |
| (Uren *et al.* 2000) | To investigate the incidence of interval nodes that are sentinel nodes and to determine the frequency with which metastatic deposits were found in these interval sentinel nodes. | Retrospective case series of 2045 patients who underwent lymphoscintigraphy over a 13 year period. | Patients with cutaneous melanoma > 1mm thick who underwent lymphoscintigraphy, with or without SLNB.<br><br>**Australia** | Incidence of interval nodes was 148 (7.2%). Interval nodes were more common where melanomas were on the trunk than on lower limbs. Micrometastases were found in 14% of interval nodes that underwent SLNB. | Incidence of metastasis is similar in interval sentinel nodes to sentinel nodes within recognised node fields. Author recommends that interval nodes should be excised along with sentinel nodes in node fields and notes that some patients the interval node is the only node with metastatic disease. | 21 patients had interval node excised as SLNB with 3 found to have metastatic deposits [small numbers]. Some patients included who were seen prior to when SLNB was described. Appraised as prognosis study (Badenoch and Heneghan, 2002). | 3 |
| (van Poll *et al.* 2005) | To evaluate whether performing SLNB in patients with melanoma increases the incidence of in-transit recurrence. | Retrospectively analysed case series of patients treated at a single institution between 1991 and 2000 according to 3 protocols: wide local excision (WLE) only (n=1035), WLE plus SLNB (n=754), and WLE plus elective lymph node dissection (n=229). | 2018 patients with primary melanomas ≥1.0 mm thick.<br><br>**Australia** | Rates of in-transit recurrence. | The incidence rates of in-transit recurrence for the three protocols were:<br>WLE: 4.9%<br>WLE plus SLNB: 3.6%<br>WLE plus elective dissection: 5.7%.<br><br>There were no significant differences between these values.<br><br>As a first site of recurrent disease the incidence rates were:<br><br>WLE: 2.5%<br>WLE plus SLNB: 2.4%<br>WLE plus elective dissection: 4.4%.<br><br>There were no significant differences between these values. | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | The subset of patients who were node positive after SLNB and after elective lymph node dissection also had similar in-transit recurrence rates (10.8% and 7.1%, respectively; p = 0.11).<br><br>On multivariate analysis, primary tumour thickness and patient age predicted in-transit recurrence as a first recurrence, but type of treatment did not.<br><br>Patients who underwent WLE only and who had a subsequent therapeutic lymph node dissection (n = 149) had an in-transit recurrence rate of 24.2%, compared with 10.8% in patients with a tumour-positive sentinel node treated with immediate dissection (n = 102; p=.03).<br><br>Authors conclude that performance of SLNB in patients with melanoma treated by WLE does not increase the incidence of in-transit recurrence. | | |

## Lymph node clearance in melanoma

### The questions

*In patients with primary melanoma what is the effect of lymph node clearance on survival?*

*In patients with primary melanoma what is the effect of lymph node clearance on lymph node recurrence and/or local recurrence?*

*In patients with primary melanoma what is the effect of lymph node clearance in terms of lymphoedema?*

### The nature of the evidence

Seven studies were identified, as follows:

- One systematic review of good quality
- One RCT of good quality
- Three observational studies of good quality
- Two clinical guidelines of good quality

Three studies originate from the UK and one study is produced collaboratively between the UK and Italy. The remaining three studies originate one each from Germany, Australia and the US. Applicability to the UK is limited.

Four studies are of patients with primary melanoma with no clinical evidence of metastasis at outset whereas the two clinical guidelines address the treatment of patients with melanoma at all disease stages.

### Summary of the supporting evidence for the recommendations

**Observational study evidence suggests that the status of the regional node basin is a strong predictor of survival, along with primary tumour characteristics such as Breslow thickness and ulceration. Systematic review and RCT evidence does not demonstrate that elective lymph**

**node dissection carries a survival benefit over a policy of observing patients with primary melanoma after wide excision. However the systematic review by Lens et al. (2002a) suggests that some patients will benefit from elective lymph node dissection.**

**Evidence based clinical guidelines from the UK recommend that in patients with melanoma, the presence of disease in one node indicates radical lymph node dissection but that elective lymph node dissection in the absence of lymph node disease should not be performed.**

**Observational study evidence suggests that the prevalence of lymphoedema amongst patients who have undergone complete level I-III axillary lymph node dissection for melanoma is 10%, and 53% after additional axillary radiotherapy.**

- The systematic review by Lens et al. (2002a), calculated a pooled odds ratio for overall mortality as 0.86 in favour of elective lymph node dissection over delayed lymph node dissection at the onset of clinical symptoms (95% CI 0.68-1.09). The authors concluded that although the result was not statistically significant and although the primary studies had flaws, the possibility exists that some subgroups of patients with melanoma will benefit from elective lymph node dissection.

- The RCT by Cascinelli et al. (1998) compared elective versus delayed regional lymph node dissection in patients with melanoma and found that the routine use of immediate node dissection had no impact on survival (hazard ratio 0.72, 95% CI 0.5-1.02), whilst the status of regional nodes affected survival significantly. The authors concluded that regional node dissection offers increased survival in patients with node metastases only.

- The retrospective, case series study by Kretschmer et al. (2005) found that overall survival at 5 years in patients who underwent delayed lymph node dissection following initial wide excision of melanoma was 37.4%. Disease free survival in this group of patients was 11.6%.

- Evidence based guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists state that elective lymph node dissection is not indicated in patients with melanoma and clinically negative lymph nodes.

- Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that in patients with melanoma, the presence of disease in one node indicates radical lymph node dissection but that elective lymph node dissection in the absence of lymph node disease should not be performed.

- The prospective case series study by Starritt et al. (2004) found lymphoedema prevalence for patients to be 10% after complete level I-III axillary lymph node dissection for melanoma and 53% after additional axillary radiotherapy. Lymphoedema was defined as an increase in arm volume greater than 16% of the volume of the control arm. The authors cited from their review of the literature that the prevalence of lymphoedema in patients with melanoma who undergo axillary lymph node dissection is reported with range 0% to 12 %.

- White et al. (2002) studied a case series of 2505 patients with melanoma and occult lymph metastases and found that the number of positive lymph nodes was the most powerful predictor of overall and recurrence free survival. Primary tumour ulceration and thickness were also powerful predictors of overall and recurrence free survival. The authors concluded that aggressive surgical therapy for regional lymph node metastases is warranted.

## EVIDENCE TABLE 4.7

***In patients with primary melanoma what is the effect of lymph node clearance on survival?***

***In patients with primary melanoma what is the effect of lymph node clearance on lymph node recurrence and/or local recurrence?***

***In patients with primary melanoma what is the effect of lymph node clearance in terms of lymphoedema?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Cascinelli *et al.* 1998) | To evaluate the efficacy of elective regional node dissection in patients with primary melanoma on the trunk. | RCT<br>Patients with primary trunk melanoma were randomised into 2 groups i) wide excision and elective regional lymph node dissection versus ii) wide excision and delayed excision (at onset of clinical signs of node metastases). | Patients <65 years, with primary melanoma on the trunk, Breslow thickness 1.5mm or greater and no clinically visible metastases.<br><br>**Italy, UK** | Percentage survival at 5 years between two groups randomised, with comparison also by regional lymph node status identified by elective (early) dissection or delayed dissection following onset of clinical signs. | 5 year survival in patients with occult regional node metastases identified was 48% [95% CI 28.0-65.8] and 26.6% [95% CI 13.4-41.8, p = 0.04] in patients in whom the regional node dissection was delayed until the onset of clinical symptoms. Multivariate analysis showed that the routine use of immediate node dissection had no impact on survival (hazard ratio 0.72, 95% CI 0.5-1.02), whilst the status of regional nodes affected survival significantly (p = 0.0007). The patients with regional nodes that became clinically and histologically positive during follow-up had the poorest prognosis. The study found that regional node dissection offers increased survival in patients with node metastases only, and points to the | | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | potential usefulness of sentinel node biopsy as a tool to ascertain which patients require further regional node clearance. | | |
| (Kretschmer *et al.* 2005) | To evaluate recurrence of melanoma following SLNB compared with that following delayed lymph node dissection in patients with clinically palpable lymph nodes. | Retrospective case series analysis using Kaplan Meier plots with recurrence as end points. | 443 consecutive patients with melanoma who met the criteria for SLNB at the time of diagnosis: 244 patients who underwent SLNB and 199 controls who received delayed regional lymphadenectomy.<br><br>**Germany** | locoregional cutaneous metastases, both as first recurrence and overall. Overall survival and disease free survival. | Overall survival at 5 years differed significantly between SLNB negative (90.1%), SLNB positive (54.4%) and delayed lymph node dissection (37.4%) groups. Disease free survival differed significantly between SLNB negative (77.7%), SLNB positive (38.6%) and delayed lymph node dissection (11.6%) groups. The median interval from primary tumour excision and nodal recurrence was 12 months for patients with delayed lymph node dissection. This was compared with patients with positive SLNB, in whom the interval from excision of primary tumour to first nodal or (mostly) distant recurrence was 47.5 months ($p < 0.00001$). | Includes loco-regional recurrence that were not first recurrences, but excludes recurrences that were excised along with the primary tumour and also those arising in the scar of previous lymphadenectomy. Longer follow-up observed in control group to SLNB group. Confounding factors analysed between positive SLNB and delayed dissection groups: only Breslow thickness significantly predicted locoregional recurrence. | 3 + |
| (Lens *et al.* 2002b) | To determine whether elective lymph node dissection (ELND) in patients with melanoma without clinically detectable regional metastases decreases overall mortality. | Systematic review and meta-analysis of randomised controlled trials comparing elective lymph node dissection with delayed lymphadenectomy at the time of clinical recurrence or no lymphadenectomy. | 1533 subjects in included trials: patients with AJCC stage I and II melanoma without clinically detectable regional metastases. 768 were assigned to ELND and 765 to delayed lymphadenectomy or no treatment.<br><br>**UK** | Overall mortality in treatment groups as compared with control groups at the end of a 5-year follow-up period. | The pooled odds ratio for overall mortality for the 3 trials was 0.86 in favour of ELND. (95% confidence interval, 0.68-1.09). Results are statistically nonsignificant, but they have potential clinical significance. The authors conclude that this systematic review of randomised controlled trials comparing elective lymph node dissection with surgery delayed until the time of clinical recurrence shows no significant overall survival benefit for patients undergoing elective lymph node dissection. Trials included in this review, however, contain significant bias. The question is not answered for all patients, and the results do not exclude the possibility that some subgroups may benefit from elective lymph node dissection. Further research is required. | Randomised controlled trials available by February 2001 included. Three randomised controlled trials met the inclusion criteria. Authors cite Cochran et al. (2000), noting that 20% of patients who undergo ELND at the time of resection of primary stage I melanoma have regional node metastasis. There was no significant heterogeneity between trials ($p = 0.41$) although there were flaws in methodology e.g. not all trials used lymphoscintigraphy. | 1 ++ |
| (Roberts *et al.* 2002) | To provide evidence | Evidence based | Patients with | Guidelines discuss | There is no role for elective lymph node | 60 references cited. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | based recommendations treatment of patients with melanoma. | guidelines, with recommendations graded according to the quality of evidence available. | melanoma. | available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | dissection in clinically node negative patients. | Scale for strength of evidence and grade of recommendations included. | |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Recommendations for practice. | The presence of disease in one node indicates radical lymph node dissection, which requires complete and radical removal of all draining lymph nodes to allow full pathological examination and should be undertaken only by surgeons with appropriate expertise.<br><br>Elective lymph node dissection should not be performed. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |
| (Starritt *et al.* 2004) | To define appropriate criteria for assessing the presence of lymphoedema using a water displacement technique, and to report the prevalence and risk factors for development of upper limb lymphoedema after level I-III axillary dissection for melanoma. | Prospective case series study, defining lymphoedema and comparing prevalence between patients treated with axillary lymph node dissection versus those with axillary dissection plus radiotherapy. | 107 patients (82 male, 25 female) who had previously undergone complete level I-III axillary dissection for melanoma of the arm.<br><br>Of the 107 patients, 17 had also received postoperative axillary radiotherapy.<br><br>Median age at measurement 56.9 years (range 27-86 years).<br><br>**Australia** | Classification and regression tree (CART) analysis was used to determine a threshold fractional arm volume increase above which volume changes were considered to indicate arm lymphoedema.<br><br>Prevalence of arm lymphoedema based upon the above.<br><br>Patients' reported symptoms gathered by | Based on the CART analysis results, lymphoedema was defined as an increase in arm volume greater than 16% of the volume of the control arm.<br><br>Using this definition, lymphoedema prevalence for patients was 10% after complete level I-III axillary dissection for melanoma and 53% after additional axillary radiotherapy.<br><br>Radiotherapy (OR 14.3, 95% CI 2.8-75.0, $p < 0.01$) and wound complications (OR 9.1, 95% CI 2.2-36.8, $p < 0.01$) were independent risk factors for the development of lymphoedema.<br><br>45% of all patients perceived an increase in the size of the arm on the side of the dissection and 31% considered that they had functional | Authors report a lack of threshold criteria to define lymphoedema in clinical practice and that prevalence of lymphoedema in this patient population is reported in the literature with range 0% to 12 %.<br><br>90 patients had undergone axillary dissection only and 17 had received adjunctive radiotherapy in addition.<br><br>Change in volume of the arm on the side of the dissection was referenced to the volume of the other (control) arm. Volume measurements were corrected for the effect of handedness using corrections derived from a control group. | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | questionnaire. | deficit in this arm, although there was poor correlation between reported deficit and lymphoedema measurement (r = 0.24).<br><br>Authors recommend that an arm volume increase of greater than 16% of the volume of the control arm be used to objectively define lymphoedema. | Effect of left / right handedness assessed using 21 healthy volunteer controls: the dominant arm was found to have 2.5% greater volume than the other arm.<br><br>Measurements were carried out median 36.4 months from the date of axillary node dissection. | |
| (White *et al.* 2002) | To describe the long term outcomes (recurrence and survival) in patients with node positive melanoma. | Retrospective review of 2505 patients treated at a single centre. | Patients with: single primary melanoma, histological confirmation of lymph metastasis but no clinical evidence of distant spread and documented evidence of full lymph node dissection within 6 weeks of confirmed lymph node disease.<br><br>**US** | Overall and recurrence free survival rates calculated. Overall survival at 5, 10, 15 and 20 years were 43%, 35%, 28% and 23% respectively. | Number of positive lymph nodes is the most powerful predictor of overall and recurrence free survival. Primary tumour ulceration and thickness were also powerful predictors of overall and recurrence free survival. The most common site of first recurrence after lymph dissection was distant (44% of all patients). Author concludes that aggressive surgical therapy for lymph node metastases is warranted and that adjuvant therapy should be individually considered. | 706 patients excluded due to no documented lymph node dissection. Patient with in-transit disease included. Patient characteristics described. | 3 ++ |

**The questions**

*In patients with SCC what is the impact of SLNB on survival?*

**The nature of the evidence**

Four studies were identified as follows:

- One clinical guideline of good quality
- Three observational studies, one of fair quality and two of poor quality.

One study is from the UK, two studies are from the US and one study is from Turkey. Applicability to the UK is therefore poor. The studies include samples of patients with primary and recurrent SCC, where one study restricts to patients with SCC of the lower lip.

**Summary of the supporting evidence for the recommendations**

**Clinical guidelines from the UK state that the role of SLNB has not been established in the management of patients with SCC.**

**There is a small volume of low quality evidence from observational studies, to suggest a role for SLNB in staging disease in patients with SCC. This evidence suggests that patients with disease-negative sentinel nodes may be spared further surgery and that SLNB may be feasible for patients with large SCC tumours of the lip. Very little survival information is provided by the studies identified, although the small study by Reschly et al. (2003) demonstrated that 5 patients with high risk SCC and negative sentinel node identified by SLNB survived without further surgery at median follow-up of 8 months.**

- A small case series study by Altinyollar et al. (2002) concluded that the SLNB may be feasible for patients with large (2.0 – 4.0 mm) SCC of the lower lip without clinically palpable lymph nodes.
- Cherpelis et al. (2002) characterised non metastatic SCC tumours according to their tendency to metastasise and recommended the use

of SLNB for staging and early detection of metastasis in patients with high risk SCC.

- Clinical guidelines on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons undertaken by Motley et al. (2003) state that the role of SLNB has not been established in the management of patients with SCC.

- A small observational study undertaken by Reschly et al. (2003) found that 5 out of a total of 9 patients had negative sentinel nodes identified by SLNB. These 5 patients were alive at follow-up of mean 13 months, median 8 months and were spared further therapy. The study was limited by small size and short follow-up; however the authors concluded that SLNB may prove to have an important role in the management of high risk cutaneous SCC patients.

# EVIDENCE TABLE 4.8

## *In patients with SCC what is the impact of SLNB on survival?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Altinyollar *et al.* 2002) | To study the feasibility of SLNB for large SCC tumours of the lower lip (2-4 cm) and no clinically palpable regional lymph nodes. | Small case series study. | 20 patients with SCC tumours of the lower lip 2-4 cm in size without clinically palpable regional lymph nodes.<br><br>**Turkey** | Evaluation of SLNB as a technique - ability to detect sub-clinical metastasis, false, negative rate, false positive rate. | SLNs were identified in 18/20 patients (80%). 3/18 patients showed sentinel node metastases (16.6%). Of the three patients with positive SLNB, all of whom underwent regional lymph node dissection, one had further regional lymph node deposits and two did not. No false negativity or false positivity was seen from SLNB. Considering the total of sentinel and non sentinel excised nodes (n = 440), 3 SLNs were metastatic (10.34%) compared with 3 (0.73%) non sentinel nodes. Authors conclude that the technique may be feasible in this setting although further study is warranted. | 3 patients were female and 17 male. Median age was 66 years (range 39-72 years). NB: All patients underwent SLNB and Regional lymph node clearance during the same procedure (specifically, bilateral suprahyoid dissection). Blue dye alone was used, not radio colloid. | 3 - |
| (Cherpelis *et al.* 2002) | To characterise SCC tumours with the greatest tendency to metastasise. | Retrospective prognostic study of 25 cases of metastatic SCC and 175 cases of non metastatic SCC, referred to a tertiary centre over a 10 year period. | Patients with primary or recurrent SCC analysed post treatment with Mohs micrographic surgery.<br><br>**US** | Outcome measure is strength of correlation between metastasis and tumour characteristics. | Tumour size >2cm [$p < 0.004$], poor differentiation [$p<.01$], presence of small tumour nests or infiltrative tumour strands [$p < 0.001$], single cell infiltration [$p < 0.001$], perineural invasion [$p < 0.001$], acantholysis [$p < 0.006$] and recurrence correlated with metastasis. Location, ulceration, inflammation and Breslow depth did not correlate with metastasis. Author recommends use of SLNB for staging and early detection of metastasis in patients with high risk SCC. | Appraised with prognosis study checklist by Badenoch and Heneghan (2002). Researchers unable to determine Breslow thickness in 12 of 25 metastatic tumours, which may have affected power. Small study size. Possible referral bias affecting incidence of metastasis of 12.5%. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Motley *et al.* 2003) | To provide evidence based guidelines on the treatment of patients with SCC on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons. | Clinical guidelines. | Patients with SCC.<br><br>**UK** | Recommendations for clinical practice. | Authors report that the role of SLNB has not been established in SCC. | 82 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Reschly *et al.* 2003) | To report the experience of a single institution with SLNB in the management of patients with high risk SCC. | Report of a case series of 9 patients with predominantly trunk and extremity high risk SCC who underwent lymphoscintigraphy and SLNB from 1995 to 2001. | Patients with high risk, histologically confirmed cutaneous SCC and clinically negative lymph nodes.<br><br>**US** | Outcomes of interest are course of disease, survival and impact of SLNB on management decisions. | Histologically positive sentinel nodes were found in 4 of 9 patients. Two of these 4 patients died of metastatic disease within two years, with no evidence of clinical regional disease. 3 of these 4 patients underwent therapeutic lymph node dissection. All 5 patients with negative sentinel nodes are alive with follow-up mean 13 months, median 8 months. These 5 patients were spared further therapy. Author concludes: Sentinel lymphadenectomy may prove to have an important role in the management of high risk cutaneous SCC patients. | Appraised with prognosis study checklist by Badenoch and Heneghan (2002). Author acknowledges - small study size with short follow-up and no controls. | 3 - |

## Imaging techniques

### The questions

*In the management of patients with malignant melanoma what is the usefulness of Positron Emission Tomography?*

*In the management of patients with malignant melanoma what is the usefulness of conventional imaging techniques compared to clinical examination?*

### The nature of the evidence

Twenty six studies were identified as follows:

- Two systematic reviews of good quality, one of which provided a meta-analysis
- Nineteen observational studies, six of good quality, eight of fair quality and five of poor quality
- Two clinical guidelines of good quality
- Three expert reviews, one of good quality and two of fair quality

Three studies originate from the UK. Six studies are from North America, three are from Australia and fourteen studies are from non UK, Western European countries. Applicability to the UK is low. One study is of oncology patients and the remainder all address patients with melanoma.

### Summary of the supporting evidence for the recommendations

**Evidence based guidelines from the UK recommend that imaging is not normally indicated in the initial assessment of patients with primary melanoma except for clinical investigation of symptoms or signs.**

### Positron Emission Tomography (PET)

**Estimates of sensitivity and specificity for PET scanning in detecting melanoma metastases vary widely according to use in different settings. Evidence from a systematic review and meta-analysis estimated sensitivity as 0.79 [95% CI 0.66-0.93], specificity as 0.86 [95% CI 0.78-0.95] and diagnostic odds ratio as 33.1 [95% CI 21.9-54.0].**

**Evidence from observational studies suggests that PET has the potential to detect surgically resectable metastases earlier than conventional imaging but is inferior to CT or MRI in detecting pulmonary and hepatic metastases from haematogenous spread.**

**The same level of evidence suggests that PET is of little use in baseline staging in AJCC stage I and II melanoma and also in the detection of lymph node metastases < 5mm in size and that smaller lymph node metastases are more likely to be identified by sentinel node biopsy.**

**One expert review concludes that the best application of whole body PET is in the management of patients with AJCC stage III and IV disease, where surgical decisions may change due to further information provided by PET.**

- The expert review by Benk et al. (2004) stated that PET may be superior to conventional imaging and follow-up although PET is limited in its ability to detect small (<5mm) nodal metastases

- The retrospective study by Damian et al. (1996) concluded that PET has the potential to detect metastases earlier than other imaging modalities, but that PET did not detect metastases which were size 1cm or less.

- The retrospective study by Dietlain et al. (1999) concluded that PET is inadequate for detecting melanoma metastases in the brain and that the possible advantages of PET appear to be in the detection of lymph or skeletal metastases. PET underestimated the number of pulmonary and hepatic metastases compared to CT

- The prospective case series study by Fink et al. (2004) concluded that PET is not sufficiently sensitive to detect lymph node metastases in patients with Stage I and II melanoma.

- The expert review by Ghersi et al. (2005) concluded that PET may give improvement in diagnostic accuracy of metastatic lesions, and can identify patients for whom surgery may achieve local disease control.

- The case series study by Gulec et al. (2003) concluded PET is a sensitive imaging modality and that PET results can change the management of patients i.e. cancelled procedure, additional surgery and by prompting non surgical treatment. In 6 patients PET detected lesions outside the field of MRI and CT.

- The prospective case series study by Hafner et al. (2004) found that PET does not have high sensitivity in detecting regional lymph node spread at baseline staging of patients with melanoma and that since smaller metastases (<4mm) can only be diagnosed by SLNB the value of whole body staging at baseline remains limited.

- The expert review by Macapinlac (2004) concluded that the best application for whole body FDG PET imaging is in stage III or IV melanoma to indicate surgical resection.

- The systematic review by Mijnhout et al. (2001) provided a meta-analysis estimate of PET sensitivity as 0.79 [95% CI 0.66-0.93], specificity 0.86 [95% CI 0.78-0.95], diagnostic odds ratio 33.1 [95% CI 21.9-54.0].

**Ultrasound (US)**

**Evidence from a systematic review and meta-analysis suggests that US has significantly higher discriminatory power to evaluate the status of lymph nodes in patients with melanoma, compared with palpation alone with odds ratios of 1755 (95% CI 726 - 4238) and 21 (95% CI 4 - 11) respectively (p = 0.0001).**

**Observational studies vary in their conclusions as to whether US is superior to palpation in detecting lymph node metastases, and provide estimates of sensitivity of US with range 86.6% - 99.2% and specificity of US with range 74.3% - 98.3%.**

- The systematic review and meta-analysis by Bafounta et al. (2004) found that US had significantly higher discriminatory power compared with palpation with odds ratios of 1755 (95% CI 726 - 4238) and 21 (95% CI 4 - 11) respectively (p = 0.0001). Positive likelihood ratios were 41.9 (95% CI 29 - 75) and 4.55 (95% CI 2 -18), and negative likelihood ratios were 0.024 (95% CI 0.01 - 0.03) and 0.22 (95% CI 0.06 - 0.31) for US and palpation, respectively. Authors conclude that US is better than palpation in diagnosis of lymph node invasion in patients with melanoma.

- The case series study by Basseres et al. (1995) found that in follow-up, abdomen ultrasonography revealed only 10% of relapses and was less effective than clinical examination.

- The prospective case series study by Blum et al. (2000) found that detection of subcutaneous and lymph node metastases was clearly improved by the use of ultrasound.

- The prospective case series study by Hafner et al. (2004) concluded that US is not sensitive in detecting regional lymph node spread at baseline staging.

- The retrospective study by Hoffman et al. (2002) found clinical examination to be superior to lymph node US at staging and follow-up of patients with melanoma, although US was the best performing imaging procedure.

- The prospective case series study by Rossi et al. (1997) found that the efficacy of US was higher than physical examination alone.

- The diagnostic study by Tregnaghi et al. (1997) found that US had sensitivity 86.6% and specificity 74.3% in diagnosing superficial lymph node metastases.

- The prospective case series study by Uren et al. 1999) found that in patients with palpable lymph nodes US was highly accurate in predicting lymph node tumours with a sensitivity of 94%, specificity 87% and accuracy 89%.

- The prospective case series study by Voit et al. (2001) found that in detecting regional tumour recurrence US had sensitivity 99.2%, specificity 98.3%, PPV 83.3 % and NPV 99.9%, and was superior to physical examination

**Computed Tomography**

**Evidence from observational studies does not support widespread, routine use of CT in the management of patients with melanoma, since CT infrequently identifies metastatic disease, although use of the technique may be warranted on an individual basis.**

**The same level of evidence suggests that CT imaging can have sensitivity 86% and specificity 100% for evaluating cervical nodes in patients with melanoma of the head or neck Johnson et al. (1997) and that information provided by CT can alter patient management.**

- The case series study by Basseres et al. (1995) found that CT scans were not useful in the follow-up of patients with stage I melanoma.

- The retrospective case series study by Hofmann et al. (2002) recommended the omission of CT scanning of the head during the initial staging of patients with melanoma.

- The retrospective case series study Johnson et al. (1997) found that routine CT head and body scanning infrequently identified metastatic disease, but did alter the management of some patients.

- The retrospective case series study by Khansur, Sanders, and Das (1989) concluded that there is no role for routine evaluation by CT in the workup for patients with stage I and II melanoma.

- The retrospective case series study by Kuvshinoff, Kurtz, and Coit (1997) concluded that CT scanning in patients with stage III melanoma should not be routinely indicated.

- The expert review by Macapinlac (2004) recommended that studies of synergistic PET/CT be undertaken.

- The retrospective case series study by Van den Breke et al. (1998) found that in patients with melanoma of the head and neck, CT of cervical lymph nodes had sensitivity 86% and specificity is 100% but was unable to detect small metastases.

## EVIDENCE TABLE 4.9

***In the management of patients with malignant melanoma what is the usefulness of Positron Emission Tomography?***

***In the management of patients with malignant melanoma what is the usefulness of conventional imaging techniques compared to clinical examination?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bafounta *et al.* 2004) | To assess the contribution of US compared with palpation in the detection of lymph node invasion in patients with melanoma. | Systematic review and meta-analysis. | A total of 6642 patients with AJCC stage I to IV melanoma.<br><br>**Review undertaken in France** | Sensitivity, specificity and positive and negative likelihood ratios calculated from the published data and interpreted on a sROC curve. | The ROC curves indicated that US had significantly higher discriminatory power compared with palpation with odds ratios of 1755 (95% CI 726 - 4238) and 21 (4 - 11) respectively (p = 0.0001). Positive likelihood ratios were 41.9 (29 - 75) and 4.55 (2 -18), and negative likelihood ratios were 0.024 (0.01 - 0.03) and 0.22 (0.06 - 0.31) for US and palpation, respectively. Authors conclude that US is better than palpation in diagnosis of lymph node invasion in patients with melanoma and has the qualities of a good diagnostic test: accuracy, absence of | Comprehensive search and study selection criteria. 12 studies met all selection criteria and were included in the meta-analysis. Effect of variability of study design not undertaken due to inadequate number of studies to provide sufficient statistical power. Authors appear to be referring to *diagnostic* odds ratio as a measure of discrimination between affected and non affected subjects (nodes). | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | adverse effects, dangerous target lesion, effective surgical resection and provides useful information. | | |
| (Basseres *et al.* 1995) | To assess the cost-effectiveness of surveillance after resection of a stage I melanoma. | Case series. | 528 patients with stage I melanoma regularly followed up in a dermatology department 1981-1991.<br><br>**France** | Relapse rate. | 115 out of 528 relapsed; 33% were detected by the patient himself, 16% by the referring physician and 39% were detected in our department. Chest X-ray or abdomen ultrasonography revealed only 10% of relapses; CT scans were useless. There was a huge gap between the cost-effectiveness of clinical examinations and radiology. The time between relapse and the last check-up in the department was less than 4 months in one third of the metastases Authors conclude that In stage I melanoma, only clinical examination is really cost-effective in the detection of metastases. However, many metastases are likely to become prominent between two examinations if patients are examined less than 3 times a year. A progressive decrease in frequency is thus not advisable, until the risk is considered low enough to stop follow-up. | | 3 |
| (Benk *et al.* 2004) | In an update to an earlier report, this | Expert review | Newly diagnosed patients with high | From 4 cited studies of staging | The review finds that PET may be superior to | Discussion/'Clinical update' review of few (4) | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | review focuses on clinical applications of PET among 6 commonly occurring categories of cancer, including malignant melanoma. Results are presented in terms of staging of new tumours and follow-up. | Diagnostic studies selected on basis of: English language, citing primary data, peer reviewed, with 12 or more subjects. 4 studies included on melanoma, Grade B evidence [VA and NHS Health Technology Assessments, Canada]. | risk melanoma and follow-up patients with previous melanoma.<br><br>**Canada** | melanoma, PET sensitivity range: 91.7-100%, specificity range: 56-97.7%, PPV range: 86-95.6%, NPV range 83-95.5%. | conventional imaging (e.g. CT, Ultrasound, MRI) and follow-up (e.g. clinical examination, radiography, CT, ultrasound and serum profiles). However, PET is limited in its ability to detect small (<5mm) nodal metastases. | studies relevant to melanoma. Studies cited are Rinne (1998), Crippa (2000), Reinhardt (2002) and Eigtved (2000). | |
| (Blum *et al.* 2000) | To assess the sensitivity and specificity of ultrasound versus clinical diagnosis in the detection of regional and subcutaneous metastases. | Prospective diagnostic study of a case series of 1288 patients evaluated at a single centre. Clinical examination preceded ultrasound. | Patients with excised melanoma.<br><br>**Germany** | Sensitivity and specificity. | Ultrasound sensitivity 89.2% and specificity 99.7%. In all histologically confirmed metastases US had revealed suspicious lesions. Clinical examination had sensitivity 71.4% and specificity 99.7%. False positive rate of US was 6.1%. Author reports: detection of subcutaneous and lymph node metastases was clearly improved by the use of ultrasound, which should be part of routine follow-up. | Patient characteristics reported. 56 patients did not undergo surgery due to rejection or advanced disease. 90.9% of US positive findings were histologically confirmed. Clinical examination preceded ultrasound. | 3 |
| (Damian *et al.* 1996) | To report on the usefulness of PET in the first 100 patients scanned at an institution as compared to all other available results (X ray, CT, MR, bone scintigraphy, | Retrospective case series based on 100 consecutive patients with a total of 133 PET scans. | Patients with melanoma for whom PET scan was indicated (to assess suitability for surgery or evaluate response to treatment). Patients had very | Various outcome measures used including time between PET and conventional detection, and detection rate (%) compared with conventional means. | PET detected 388 (93%) out of 415 radiologically, clinically or histopathologically confirmed metastases. PET did not detect 16 metastases which were 1cm or less, static or regressing, with a false negative rate of 6.7%. In | Patients differ in disease stage, extent of body scanned and combination of comparative diagnostic tests performed. Lesion clusters were counted as single foci. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | clinical findings, and histopathology). | | variable stages of disease, from primary lesion only to widespread metastases.<br><br>**Australia** | | 20 patients PET detected metastases that were not detectable by the comparative methods until 6 weeks to 6 months later. PET findings influenced the management of 22 patients. Author concludes: PET has the potential to detect metastases earlier than other imaging modalities. | | |
| (Dicker *et al.* 1999) | To evaluate 5-year follow-up in patients with melanoma. | Case series; cross-sectional survey. | 1568 patients on SE Scotland melanoma database with stage 1 melanoma excised1979-1994.<br><br>**UK** | Recurrence; method of detection; patient practices. | 293 (19%) developed a recurrence, 32 had a 2nd primary melanoma and 97 had an in-situ melanoma. Disease-free interval shortened progressively with increasing tumour thickness. 80% of recurrences were within 1st 3 years, but a few patients (< 8%) had recurrences 5 or 10 years after initial surgery. In-situ melanomas did not recur. 47% of recurrences were noted 1st by patients, and only 26% were detected 1st at a follow-up clinic. 89% were still under review when their recurrences were detected, and 65% had been seen within the previous 3 months. Questionnaires were completed by 120 patients: sun protection and avoidance, and mole examination were more likely after melanoma excision. | Authors recommend 3-monthly review of patients with invasive lesions for the first 3 years. Then, those with lesions >/= 1.0 mm need 2 further annual reviews. Patients with in-situ lesions should be reviewed once, to confirm adequate excision (0.5 cm margins) and to give appropriate education. Surveillance beyond 5 years is only justified if there are special risk factors. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Dietlein *et al.* 1999) | To investigate the role of PET in staging compared to routine radiological examinations and also whether indications for PET may be optimised. | Retrospective comparison of original PET images with US, CXR, CT, skeletal scintigraphy and MRI (undertaken within 2 weeks of PET). 68 patients analysed (91 PET scans). In each case the PET scan was indicated on clinical grounds, not by trial protocol. | Patients with melanoma where lymph or haematogenous metastases were known or suspected i.e. high risk/advanced stage patients.<br><br>**Germany** | PET results evaluated in multivariate tables by different scan combinations noting: additional foci identified in organs and additional information supplied by PET. | PET underestimated the number of pulmonary and hepatic metastases compared to CT. PET is inadequate for detecting metastases in the brain. Possible advantages of PET appear to be in detection of lymph or skeletal metastases. PET can only be recommended once haematogenous metastasis in the lungs and abdomen has been excluded by CT or MRI. | Author acknowledges weakness of design whereby patients received scans by clinical need rather than trial protocol. Conventional tests occurred both before and after PET but within 2 weeks of PET. Numbers of metastases in comparison were not boosted by multiple scans in some patients. Frequent lack of histological evidence reported and clinical course in follow-up often used to infer true state. | 3 - |
| (Fink *et al.* 2004) | To compare FDG-PET findings with histopathological results of SLNB (as gold standard) in patients with primary melanoma AJCC stage I and II. | Prospective, diagnostic case series - all subjects receive PET then SLNB. | Patients with histologically proven melanoma with Breslow thickness > 1mm and clinically normal, sonographically inconspicuous lymph nodes i.e. AJCC stage I and II.<br><br>**Austria** | Sensitivity, Specificity, PPV, NPV of FDG PET using SLNB as gold standard. | FDG PET had sensitivity 13% [2.2-47.1%] specificity 100%, PPV 100%, NPV 85%. Author concludes: PET is not sufficiently sensitive to detect lymph node metastases in patients with Stage I and II melanoma. Low sensitivity is probably due to small size of metastatic deposits detected by SLNB. | 48 patients studied. Some patients had primary melanoma excised before the study, others during the study. | 3 + |
| (Ghersi *et al.* 2005) | To review evidence on the use of PET for several diseases, including melanoma in terms of diagnostic accuracy, clinical decision making | Literature Review based upon structured search strategy and study inclusion criteria. Findings from individual studies compared, but no pooled effects | Many patient populations considered - disease specific, although including melanoma patients with suspected | Insufficient evidence to draw definitive conclusions, however found that PET may give improvement in diagnostic accuracy of metastatic lesions and may also identify | Funding recommended for PET for preoperative evaluation of patients considered for surgery for apparently limited metastatic disease from malignant melanoma. | Not strictly a systematic review, but a review of literature designed to inform allocation of health resources.<br><br>NB cites Rinne (1998) and Damian (1996), | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | and cost effectiveness, to make recommendations for public spending decisions. Included was the specific question Can PET define the role of surgery in patients with potentially resectable metastatic disease from malignant melanoma? | calculated. | metastases.<br><br>**Australia** | patients for whom surgery may achieve local control.<br><br>Sensitivity and specificity or other performance criteria cited from 2 primary studies. | | both studies within table. | |
| (Gulec *et al.* 2003) | To evaluate the accuracy of FDG PET in determining extent of disease in patients with metastatic melanoma. | Diagnostic study of 49 consecutive patients evaluated at a single centre. Patients underwent conventional imaging (CT, MRI) followed by whole body PET (conducted blindly). Initial treatment plan defined before PET scan. 51 lesions examined by histology. | Patients with melanoma AJCC stage II, III or IV (i.e. with known or suspected regional or distant metastases).<br><br>**US** | Sensitivity, specificity, PPV, NPV and accuracy. Discussion considers whether PET changed the management from the initial treatment plan set after conventional imaging. | For lesions > 1cm: PET had sensitivity 100% specificity 75%, accuracy 97%, PPV 97% and NPV 100%. For lesions < 1cm PET had sensitivity 13%, specificity 33%, accuracy 17%, PPV 50%, NPV 7%. Where comparative tests were complete (27 patients) PET detected more lesions in 52% patients, same no. in 41% and fewer in 7%. In 6 patients PET detected lesions outside the field of MRI and CT. PET results changed the management of 24 patients (49%) i.e. cancelled procedure (12), additional surgery (6) and prompted non surgical treatment (6). Author concludes that PET is a sensitive imaging modality. | The number and type of radiographic studies undertaken varied for each patient depending on individual symptoms/physician preference. Only 27 0f 49 patients PET scanned were compared with the full battery of comparative tests, but the analysis acknowledges this. | 3 + |
| (Hafner *et al.* 2004) | To address the sensitivity and | Prospective study of 100 consecutive | Patients with newly diagnosed | Sensitivity, specificity, PPV, | PET sensitivity 8%, specificity 100%. | Author acknowledges over -representation of | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | specificity of physical and radiological baseline staging in 100 consecutive patients with primary melanoma of Breslow thickness > 1mm. | patients. All patients received US, X-ray, PET and SLNB. Discussion considers baseline staging for regional lymph nodes and distant metastasis. | primary melanoma with exclusion criteria set out for recurrence/other metastases, age > 80, pregnancy, co morbidity.<br><br>**Switzerland** | NPV. | US sensitivity 8%, specificity 88%.<br><br>Author concludes: Macroscopic regional lymph metastases >4mm can be reliably detected by physical examination and lymph node US, where needle aspiration is then indicated. Smaller metastases <4mm (including micro metastases <2mm) can only be diagnosed by SLNB. Neither US nor PET have a high sensitivity in detecting regional lymph node spread at baseline staging. The detection rate for distant metastases with imaging techniques was found to be zero and the chance of detection is postulated to be very low. The value of whole body staging at baseline remains limited. | nodular melanoma as a result of referral bias - unlikely to affect study objectives. | |
| (Hofmann *et al.* 2002) | To investigate the efficacy of imaging (abdominal / peripheral lymph node US, CT head, Chest X ray, bone scan) in screening, cost of follow-up methods in relation to screening success and the relationship | Retrospective study - 'cohort' (cases) identified from medical records of a single centre over a 16 year period. Records evaluated for staging and follow-up where criteria were met. | 661 Patients identified with melanoma stage I/II, IIIA/B and IV at time of diagnosis.<br><br>**Germany** | Efficacy: false positive, true positive, detection rates in staging and follow-up. Economics: cost per metastasis detected and efficiency ratio. Survival: analysed by mode of detection with Kaplan-Meier survival curves and log-rank test. | Patient history and clinical examination was the most successful diagnostic tool in staging and follow-up. Lymph node sonography was the best performing imaging procedure (detection rate 16% at initial staging). Clinical examination had a greater efficiency ratio than all other methods at all follow-up phases. No | Case series' rather than true cohort. Cases presented over 16 years. Patient characteristics - histological type, stage, site, age, sex similar to those of other recently conducted historical cohorts (but n = smaller) Questionnaires / interviews used to capture missing data | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | between mode of recurrence detection compared with survival. | | | | survival advantage detected between symptomatic versus asymptomatic relapses or doctor versus patient reported relapses. Recommends: omission of chest X ray abdominal US, CT head and bone scan at initial staging. In stage III patients with second relapse, frequent imaging did not give increased detection rate. | from patients or family. Appropriate use of statistics. | |
| (Hojgaard 2003) | To comment on the appropriateness of Health Technology Reports (HTAs) as a measure of the usefulness of PET as an imaging technique in the service planning setting. | Editorial - expert review. | Oncology patients.<br><br>**Denmark** | | Author notes that HTAs may both facilitate and restrict the clinical use of new technologies and that HTAs in western countries make discordant recommendations on PET, despite using the same materials and methods. Author argues that: HTA findings should be interpreted cautiously and that future PET evaluation should be scientific and not based upon HTA reports. | Expert opinion. | 4 |
| (Johnson *et al.* 1997) | To address the clinical impact of CT imaging in detecting clinically unsuspected distant metastases in patients with AJCC stage III melanoma. | Retrospective case series evaluation of 426 CT scan results (127 patients underwent at least one scan of head, chest, abdomen or pelvis) from a specialist melanoma centre within 2 months of diagnosis. | Patients with AJCC stage III asymptomatic melanoma, metastatic to the regional lymph nodes.<br><br>**US** | Evaluation by rates of false and true positive CT results by body area of CT scan and by location of regional node disease. | CT imaging revealed true positive distant metastases in 6 (6%) head, 11 (9%) chest 12 (10%) abdomen and 4 (4%) pelvis scans. False positive results were found in 0 head, 9 (8%) chest, 8 (7%) abdomen and 0 pelvis scans. False versus true positive CT results were near equal for chest and abdomen and no false | Patients presented over an 11 year period. True/false positive results verified by either biopsy findings or subsequent course of disease or further diagnostic studies. Limitations arise from retrospective design of patients necessarily managed according to clinical need. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | positives were found in CT head and pelvis. A higher percentage of true positives were found in patients with axillary/inguinal regional node disease than in those with regional node disease of head/neck. Author concludes: routine CT head and body scanning infrequently identifies metastatic disease, but can alter patient management. Further, prospective study and cost-benefit analysis recommended. | | |
| (Khansur *et al.* 1989) | To evaluate the role of metastatic workup in stage I and II melanoma and in local and regional recurrence. | Retrospective study of 143 patients evaluated for metastasis at a single centre. Patients evaluated 1-8 weeks after resection. Patients received at least 3 of radio nucleotide brain, bone and liver scan, CT head, upper GI tract - small bowel series. All patients underwent chest roentgenogram, LFT and serum LDH. | Patients with stage I, II and local or regional recurrence of melanoma.<br><br>**US** | False and True positive results considered for each scan type. | The radio nucleotide scans of brain, liver and bone, CT brain and GI tract series rarely showed a positive yield in the absence of symptoms and laboratory evidence. Author concludes: there is no role for routine evaluation by the radio nucleotide, CT and GI tract series and these should be considered by individual symptoms and laboratory evidence. Chest roentgenogram should be routinely obtained. A serum LDH > 300 U/L is a marker for tumour burden to prompt the search with imaging techniques under study. | No patient characteristics reported. Various reference standards used for comparison with each diagnostic scan evaluated - histology not always available. Patients studied over a 12 year period. | 3 - |
| (Kuvshinoff *et al.* 1997) | To determine the diagnostic yield of CT in identifying | Retrospective study of 347 patients with | Patients with AJCC stage III melanoma. | Diagnostic yield, true positives, false positives. | Individual CT scans identified 33/788 (4.2%) instances of metastatic | 142 patients excluded due to Stage IV disease, elective lymph node | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | metastases in patients with stage III melanoma. | AJCC stage III melanoma. 289 patients had at least one CT chest, abdomen or pelvis and 136 had all three CT scans. | **US** | | melanoma with false positive rate of 66/788 (8.4%). In patients with complete CT scans of head, abdomen and pelvis metastases were detected in 11/136 (8.1%). Author recommends: routine CT scanning in this patient group should not be routinely indicated. Selective CT scans according to site of regional adenopathy may be useful. | dissection or symptom directed workups. True positives evaluated by histology, cytology, autopsy or obvious clinical progression. | |
| (Macapinlac 2004) | To review the clinical utility of FDG PET and FDG PET in combination with CT imaging in lymphoma and melanoma for staging, recurrence evaluation and assessing prognosis. | Expert review/discussion paper. | Considers patients with lymphoma and patients with different stages of melanoma.<br><br>**US** | Various outcome measures of primary studies discussed, in terms of management of different disease stages. | Author notes from other studies: PET is not as effective as SLNB to evaluate patients without clinical evidence of nodal involvement. The best application for whole body FDG PET imaging is in stage III or IV (M1) melanoma to indicate surgical resection. Studies of synergistic PET/CT are recommended. | Discussion with citation from other studies. | 4 |
| (Mijnhout *et al.* 2001) | To determine the diagnostic accuracy of FDG PET in patients with melanoma (by sub groups according to disease stage). | Systematic Review including methodological quality analysis, quantitative meta-analysis and qualitative analysis and assessment of heterogeneity. | Patients with malignant melanoma. Individual studies recruited patients from different care settings and with different stages of disease.<br><br>**Review undertaken in Holland** | Qualitative: strength of evidence. Quantitative: Pooled sensitivity and specificity and diagnostic odds ratio for FDG PET. | Evidence quality in primary studies poor, with heterogeneity of studies. PET sensitivity 0.79 [0.66-0.93], specificity 0.86 [0.78-0.95], DOR 33.1 [21.9-54.0]. However study reports that higher quality evidence is required before guidelines for FDG PET may be developed for patients with melanoma. | | 1 ++ |
| (Roberts *et al.* 2002) | To provide | Evidence based | Patients with | Guidelines discuss | Stage I and IIA melanoma | 60 references cited. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | evidence based recommendations treatment of patients with melanoma. | guidelines, with recommendations graded according to the quality of evidence available. | melanoma.<br><br>**UK** | available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | patients should not be staged by imaging as the true-positive pick-up rate is low and the false-positive rate is high. This recommendation would be revised if effective therapy for visceral melanoma were identified. | Scale for strength of evidence and grade of recommendations included. | |
| (Rossi *et al.* 1997) | To ascertain the role of US of lymph node sites in the detection of metastases from melanoma, both for staging and during follow-up. | Prospective diagnostic study of a case series of 80 patients with complete follow-up (out of 85 patients treated). Each patient received staging and 6 monthly follow-up for 24 months. | Patients with melanoma with Breslow thickness 1mm or more and/or Clarke's level 3 or more.<br><br>**Italy** | Sensitivity, specificity and accuracy for palpation, US alone and US plus FNAB by anatomical site. | Sensitivity, specificity, accuracy (%) for palpation: 50/85/80 (axillary) 11/90/76 (inguinal); for US alone: 100/92/93 (axillary) 89/88/88 (inguinal); and for US + FNAB 100/100/100 (axillary) 89/100/98 (inguinal).Author concludes: efficacy of US whether combined with FNAB or not is higher than physical examination alone. US cannot detect micro metastases to the lymph nodes but is recommended for staging and follow-up in this group. | Patient characteristics reported. 5 patients excluded from study due to loss to follow-up or death before end of follow-up period therefore 80 evaluated. No confidence intervals, test statistics or p values used. | 3 + |
| (Schmid-Wendtner *et al.* 2001) | To determine the risk for development of second primary neoplasms in patients with cutaneous melanomas, including second primary melanoma and other neoplasms. | Prospective, single centre prognosis study of 4597 patients, followed up for median 7.2 years, including history, clinical examination, US lymph nodes, US abdomen and chest X ray. | Patients with excised primary melanoma at a centre treating 80% of local referrals.<br><br>**Germany** | Relative risk of development of further primary neoplasms calculated using person years method. | Patients with one cutaneous melanoma have a significant increased relative risk for the development of further melanoma (RR men 38.5 [30.4-48.1] women 29.0 [22.0-37.5]). Men with primary melanoma have increased relative risk for development of kidney carcinoma (RR 3.5 [1.4- | Study undertaken as a second objective within an existing study of melanoma progression in long term follow-up of cutaneous melanoma. Patient characteristics described; representative of population served by centre. Data on additional primary | 3++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | 7.2]). There was no significant increased risk for other neoplasms. Author emphasises value of thorough follow-up to detect further primary melanomas and also routine abdominal ultrasound in follow-up which may be of value in detecting kidney carcinoma in men. | neoplasms obtained by questioning and verified by histology reports in most cases. | |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma. | Recommendations for practice. | Chest X ray, USS and CT are not indicated in the initial assessment of primary melanoma unless indicated for clinical investigation of symptoms or signs. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |
| (Tregnaghi *et al.* 1997) | To assess the diagnostic accuracy of ultrasound evaluation of superficial lymph node of patients with melanoma and identify features permitting early detection of nodal involvement. | Prospective diagnostic study. Patients received 6 monthly scans over 1-3 year period, compared with course of disease (6 month disease free survival of interest) and cytology (by fine needle biopsy) and histology following resection of nodes where | 87 patients with resected cutaneous melanoma.<br><br>**Italy** | 32 Patients had suspect US results and were followed up with fine needle biopsy. Results classed as true positive (13), true negative (55), false positive (19), false negative (2). | In total US had sensitivity 86.6%, specificity 74.3%. If the sonographic criteria for suspect nodes are reduced to round shape without striae, alteration of cortex/medulla, nodule formation, specificity rises to 94.6% [found statistically significant with $chi^2$ test]. | Area of lymph drainage identified by clinical judgement. One patient counted twice owing to two lymph basins evaluated due to equidistant site of primary tumour. Apparent misprint of p value. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | indicated. | | | | | |
| (Uren *et al.* 1999) | To evaluate whether high resolution ultrasound could predict the presence of metastatic disease in patients with palpable lymph nodes at a follow-up clinic. | Prospective case series of 52 patients treated at a melanoma unit. Ultrasound scans undertaken of 61 regional node fields. True state determined by fine needle biopsy (n=15), excision biopsy (n=25) or clinical follow-up (n=19). | Patients with melanoma (primary tumour excised) presenting with clinically palpable lymph nodes at follow-up.<br><br>**Australia** | Sensitivity, specificity, accuracy (no statistical test or estimate of precision). | US had a sensitivity of 94% and specificity 87%, accuracy 89%. Author reports key diagnostic US features as node thickness greater than two thirds of node length and low level echoes in the node. Author found positive US result to be highly accurate in predicting lymph node tumours and recommends that further clinical follow-up is adequate given a normal US result, but states that micro metastases may not be detected. | Patients presented with clinically palpable lymph nodes. 52 patients analysed. No confidence intervals, test statistics or p values used. 2 patients lost to the study centre assumed to be normal on clinical examination by their local doctors. | 3 - |
| (Van den Breke *et al.* 1998) | To assess the value of CT scanning in detecting lymph node metastases in the neck from malignant melanoma and to look at possible CT characteristics of such metastases. | Retrospective study of 26 patients with melanoma of head/neck, shoulder or upper limb origin who received CT scans of the neck, followed by neck dissection, over a 6 year period. CT results analysed blind of pathology. | Patients with melanoma Breslow thickness 0.8-22 mm.<br><br>**Holland** | Sensitivity and specificity of palpation and CT scan together. | Sensitivity of palpation and CT scan together for the whole patient group is 86% and specificity is 100%. CT was unable to detect small metastases and is of limited value for detection of occult metastases in the neck. As both CT false positive results (n = 2) were of 8mm slices, 3-5mm slices are recommended. Author reports difficulty with CT scanning in melanoma due to lack of well defined radiological criteria. Author discusses potential impact of fine needle aspiration biopsy and also sentinel node biopsy. | Primary tumour site unknown in 5 patients. Interval from treatment of primary tumour to neck dissection 0 to 8.8 years (mean 21 months). Pathology report used as gold standard. No confidence intervals, test statistic or p value reported. | 3 |
| (Voit *et al.* 2001) | To compare the efficacy of physical | Prospective case series of 829 | Patients with melanoma | Sensitivity specificity PPV NPV. Survival | **Physical examination** | Patient characteristics reported. 6 lesions | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | examination (PE) versus regional Ultrasound B scan (UBS) for the detection of regional tumour recurrence in melanoma patients. To evaluate whether survival is affected by detected lesion size. | consecutive patients who received concomitant UBS and PE. 3011 UBS + PE carried out Patients followed up to evaluate survival. Definitive diagnosis of suspicious lesions determined by needle biopsy cytology/histology. | (median Breslow thickness of primary tumour 1.5mm) who are macroscopically disease free.<br><br>**Germany** | measured by disease free and overall survival according to detected lesion size. | Physical examination had sensitivity 25.2% [19.9-31.2%] specificity 98.4% [97.8-94.6%] PPV [57.5% [47.5-66.9%] NPV 93.8% [92.8-94.6%].<br><br>**Ultrasound B Scan**<br><br>Ultrasound had sensitivity 99.2% [97.3-99.6%] specificity 98.3% [97.7-98.7%] PPV 83.3 % [78.5-87.4%] NPV 99.9% [99.6-100%]. UBS was highly superior to PE. Overall survival was affected by the size of the largest metastatic lesion (p = 0.001) and also the number of metastatic lesions (p = 0.012). Earlier detection appears to influence survival. | detected were non melanoma malignancy and excluded from the analysis. 3 tiers of follow-up frequency set by Breslow thickness. | |

# Treatment of patients with skin cancer and premalignant skin conditions

## Melanoma

### The questions

***What is the optimal width of excision for melanoma tumours?***

### The nature of the evidence

Five studies were identified as follows:

- Two systematic reviews of good quality
- One RCT of good quality
- Two clinical guidelines of good quality

Four studies are from the UK and one study is from Canada. Applicability is reasonable, accepting that primary studies in the systematic reviews are from numerous countries. All studies relate to populations of patients with melanoma who undergo wide excision.

### Summary of the supporting evidence for the recommendations

**The definitive treatment for melanoma tumours is surgical excision. Evidence from two systematic reviews suggests that in excision of melanoma tumours, surgical margins of 3-5cm have no advantage in terms of local recurrence overall survival and disease free survival, over margins of 1-2cm [and one systematic review concluded that a 2cm margin is adequate]. Evidence from a subsequent, RCT which compared 1cm versus 3cm surgical excision margins for melanoma tumours found an advantage of borderline statistical significance in terms of locoregional recurrence for 3cm margins over 1cm margins, with no significant difference in survival detected.**

**Evidence based guidelines from the UK recommend that lesions suspicious of melanoma are initially excised as full-thickness skin biopsies including the whole lesion with a 2–5 mm clinical margin of normal skin laterally and with a cuff of sub dermal fat. Histologically confirmed melanoma tumours require referral to a specialist centre for excision, with a margin of between 1cm and 3cm, stratified according to Breslow thickness.**

- The systematic review and meta-analysis undertaken by Haigh, DiFronzo, and McCready (2003) found no statistically significant differences between wide surgical excision with margins ranging from 3-5 cm and narrower surgical excision with margins ranging from 1-2 cm with respect to mortality, disease-free survival and local recurrence rate. The authors concluded that the evidence is more supportive of a 2-cm margin than a 1-cm margin as the minimum margin of excision, and concluded that surgical excision margins no more than 2 cm around a melanoma of the trunk or extremities are adequate.

- The systematic review by Lens et al. (2002a) found that no included study showed any statistically significant difference between the patients treated with narrow versus wide excision margins with regard to recurrences and survival but concluded that current evidence is not sufficient to address the optimal surgical margins for all melanomas, and that further research is required.

- Evidence based guidelines produced by Roberts et al. (2002) on behalf of the BAD recommend that a lesion suspected to be melanoma should be initially excised as a full-thickness skin biopsy to include the whole tumour with a 2–5 mm clinical margin of normal skin laterally and with a cuff of sub dermal fat. Histologically confirmed melanoma tumours should be subsequently excised with a margin of between 1cm and 3cm, stratified according to Breslow thickness.

- Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that suspected melanoma

tumours should be initially excised with a 2mm margin and a cuff of fat and that wider excision requires referral to a specialist centre.

- The RCT by Thomas et al. (2004) studied surgery for melanoma tumours, comparing 1cm versus 3cm excisional margins and found that locoregional recurrence as a first event was more likely in the group with 1 cm margins of excision, compared to the group with 3 cm margins, with marginal statistical significance (HR 1.26, 95% CI, 1.00 to 1.59; p = 0.05). There was no significant difference in overall survival between the two groups (HR for death, 1.07; 95% CI, 0.85 to 1.36; p = 0.6).

# EVIDENCE TABLE 4.10

## *What is the optimal width of excision for melanoma tumours?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Haigh *et al.* 2003) | To determine in patients with localized primary melanoma of the trunk or extremities the optimal excision margin that achieves the highest disease-free survival and overall survival and the lowest local recurrence rate. | Systematic review and meta-analysis of RCTs<br>Inclusion criteria: RCTs or quasi-randomised clinical trials comparing 2 different margins of excision published 1966-2002<br>No exclusion criteria.<br><br>3 relevant original studies and 3 follow-up studies were included.<br><br>**Canada** | Adult(>18 years) with cutaneous melanoma of trunk or extremities with no evidence of metastasis (n= 1867).<br><br>Intervention: Surgical excision of primary melanoma. | Overall survival; disease-free survival; local recurrence; wound complications and need for skin grafting. | No statistically significant differences were found between wide surgical excision (margins ranging from 3-5 cm) and narrower surgical excision (margins ranging from 1-2 cm) with respect to: **mortality**, (4-6 years follow-up - RR 0.= 93 95% CI 0.73-1.19; 8-11 years follow-up RR = 0.95 95% CI 0.81-1.12) **disease-free survival** (55-69.6 months follow-up – RR = 1.03 95% CI 0.81-1.32; 8 years follow-up RR = 0.89 95% CI 0.72-1.09) or **local recurrence rate** (48-72 months follow-up RR = 0.98 95% CI 0.38-2.52; 8-10 years follow-up RR = 0.90 95% CI 0.41-2.00).<br><br>Only one study reported wound complications. No statistically significant differences were found.<br><br>Only one study reported need for skin grafting. There was a significant reduction in the need for skin grafting with narrow excision compared with wide excision (RR = 4.15 95% CI2.83-6.07; $p < 0.001$) Number needed to harm from wide excision is 3, with 95% CI 2.38-3.7. | Medline, Embase and Cochrane only searched. No hand-searching. No unpublished studies sought – publication bias?<br>No language restrictions<br>Data extraction and quality assessment techniques described. Methodological quality reported as good (although all lacked blinding of intervention for obvious reasons).<br>No statements about whether any of the studies were sufficiently powered to detect any effects.<br><br>Trials differed in eligibility criteria, particularly the criterion of Breslow thickness.<br><br>Authors conclude that surgical excision margins no more than 2 cm around a melanoma of the trunk or extremities are adequate; overall survival, disease-free survival and recurrence rate | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | are not adversely affected compared with a wider excision. There is more data to support a 2-cm margin than a 1-cm margin as the minimum margin of excision. Surgical margins should be no less than 1 cm around the primary melanoma.<br><br>Well-conducted systematic review but only 3 studies which appear to differ in eligibility criteria. | |
| (Lens *et al.* 2002a) | To describe published evidence and determine effectiveness of wide surgical margins compared with narrow surgical margins. | Systematic review of RCTs to 2001:<br>Inclusion: RCTs comparing narrow v wide excision; patients with melanoma with no evidence of metastases (Stage I and II).<br><br>Meta-analyses performed for 2 outcomes: 5-year overall survival and disease-free survival.<br><br>**UK** | The included trials (4) comprised 2406 patients; 1178 randomised to narrow excision v. 1228 patients randomised to wide excision.<br><br>NB definition of narrow/wide varied between studies<br>Narrow = 2cm in 3 studies; 1cm in 1study.<br><br>Wide = 5cm in 2 studies; 4cm in 1 study and 3cm in 1study. | Included in review: local recurrences as a site of first relapse; incidence of other metastases (all types) and overall and disease-free survival at end of follow-up. | Local recurrence:<br>21 (12 in narrow and 9 in wide group). Not statistically significant in and of the 3 trials including 2071 patients reporting this data (NB Definition of local recurrence varied between studies).<br><br>Metastases:<br>Rates of in-transit, regional and distant metastases not statistically significantly different in any studies.<br><br>Overall survival:<br>1979 live patients recorded (972 narrow group; 1007 wide group):<br>5-year overall survival data available for 3 trials:<br>Peto pooled OR 0.79 (95% CI, 0.61-1.04).<br><br>Disease-free survival:<br>Reported for 1854 patients (949 wide group; 905 narrow group):<br>5-year disease-free survival data available for 3 trials:<br>Peto pooled OR 0.89 (95% CI, 0.69-1.13). | Sources used: Medline, Embase, Cochrane controlled trials register.<br>Adequacy of search strategy terms?<br>Hand-searching, no language restrictions and search for unpublished data.<br>Publication bias not assessed<br>Validity of studies assessed by randomisation procedure, numbers lost to follow-up.<br>Not stated how inclusion criteria applied.<br>Not stated how judgements of validity made.<br>Two reviewers independently extracted data, any disagreements resolved by discussion.<br>Heterogeneity assessed.<br>Included studies may have been of limited quality.<br><br>Data appear to support authors' general conclusions, although lack of detail about included studies makes it difficult to assess | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | generalisability of findings: Not one of the included studies showed any statistically significant difference between the 2 groups treated with narrow or wide excision margins with regard to recurrences and survival. However, current evidence is not sufficient to address the optimal surgical margins for all melanomas, and further research is required. | |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available.<br><br>**UK** | Patients with melanoma. | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | Excision of a lesion suspected to be melanoma should be performed as a full-thickness skin biopsy to include the whole tumour with a 2–5-mm clinical margin of normal skin laterally and with a cuff of sub dermal fat.<br><br>Incisional biopsy should not be undertaken in primary care.<br><br>**Excision margins by Breslow thickness:**<br>In situ: 2–5-mm excision margin.<br><br>Clinical margins to achieve complete histological excision:<br>Breslow < 1 mm: 1 cm excision margin (narrower margins are probably safe in lesions less than 0·75 mm in depth)<br>Breslow 1–2 mm: 1–2 cm excision margin<br>Breslow 2·1–4 mm: 2–3 cm excision margin(2 cm preferred)<br>Breslow > 4 mm 2–3 cm excision margin. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Scottish Intercollegiate Guidelines Network | To provide advice to health professionals | Evidence based guidelines, with | Patients with melanoma. | Recommendations for practice. | A suspected melanoma should be excised with a 2mm margin and a cuff | Guideline development was based upon a multidisciplinary | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| 2003) | involved at all stages of care of patients with melanoma. | recommendations graded according to the quality of evidence available.<br><br>**UK** | | | of fat.<br><br>If complete excision cannot be performed as a primary procedure a full thickness incisional or punch biopsy of the most suspicious area is advised.<br><br>A superficial shave biopsy is inappropriate for suspicious pigmented lesions.<br><br>Wider excision requires referral to a specialist centre. | Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | |
| (Thomas *et al.* 2004) | To compare outcomes in 1-cm and 3-cm margins of excision of melanoma tumours 2mm or greater in thickness. | RCT<br>Intervention: Surgery with 1cm margin of excision compared with 3 cm margin of excision.<br><br>**UK** | 900 patients with melanoma:<br>1 cm margin n=453<br>3 cm margin n=447. | Local recurrences as first events; mortality; overall survival.<br><br>Median follow-up 60 months. | There were 168 locoregional recurrences (as first events) in the group with 1 cm margins of excision, as compared with 142 in the group with 3 cm margins (HR 1.26; 95% CI, 1.00 to 1.59; P = 0.05). There were 128 deaths attributable to melanoma in the group with 1 cm margins, as compared with 105 in the group with 3 cm margins (HR, 1.24; 95% CI, 0.96 to 1.61; P = 0.1); overall survival was similar in the two groups (HR for death, 1.07; 95% CI, 0.85 to 1.36; P = 0.6). | Well-designed, conducted and analysed trial to minimise biases. | 1++ |

## Non melanoma skin cancer

### Surgical treatment

### The questions

*In patients with BCC or SCC treated with surgical excision, what are the rates of positive margins?*

### The nature of the evidence

Twelve studies were identified as follows:

- One cohort study of poor quality
- Ten observational studies of fair quality
- One clinical guideline

Seven studies originate from the UK. Two studies are from the US and one study each is from Holland, New Zealand and Ireland. Applicability to the UK is reasonable. Nine studies are of patients with BCC, one study is of patients with SCC and two studies address both BCC and SCC.

### Summary of the supporting evidence for the recommendations

**Evidence from observational studies suggests that the rate of incomplete excision of BCC has range 2% to 18%, with high rates for periocular BCC. The rate of incomplete excision for SCC has range of zero to 10.1%, with high rates reported for SCC of the lip. The same level of evidence suggests that the overall local recurrence rate for SCC is 2.8% and the local recurrence rate for BCC has range 5% for completely excised tumours to 39% where excision is incomplete.**

**Evidence from one cohort study and observational studies suggest that factors associated with incomplete excision of NMSC include difficult anatomical sites on the head and neck, less experienced surgeons,**

**minimal excision margins, older patient age and invasive histological subtype.**

**Evidence from the same cohort study as above is suggestive of a role for curettage in reducing the frequency of positive margins in the management of patients with BCC.**

**Evidence based guidelines from the UK report that surgical excision is a highly effective treatment for primary BCC but that in recurrent BCC, cure rates from surgery are inferior to those for primary lesions and that wider excision margins are required for recurrent BCC tumours.**

- A prospective case series by Bisson et al (2002) comparing surgical and histological margins found the mean observed surgical margin to be 3.0 mm and the mean histological margin 3.7 mm. This study identified 4 incomplete excisions, all at the lateral margin, out of 100 BCCs excised in 86 patients treated by conventional surgical excision.

- Evidence based guidelines on the treatment of patients with BCC produced on behalf of the British Association of Dermatologists by Telfer, Colver, and Bowers (1999) report that surgical excision is a highly effective treatment for primary BCC but that in recurrent BCC, cure rates from surgery are inferior to those for primary lesions and that peripheral excision margins of 5-10 mm may be required for recurrent BCC. The management of incompletely excised BCC remains controversial since some studies report that not all incompletely excised BCC tumours recur.

- Chiller et al (2000) found that in patients with excised BCC, risks for tumour margin involvement included head and neck lesions (P<.001), lesions treated by physicians performing fewer than 51 procedures (P<.001), and invasive subtypes (P<.01). Factors associated with surgical failure in SCC included in situ disease (P=.01) and an older (77 vs. 74 years) patient population (P=.05). This study concluded that curettage decreases the frequency of positive margins in the management of BCC but not of SCC.

- A prospective case series by de Visscher et al (2002) found that in patients with SCC of the lower lip, the local recurrence rate was 2.8% and the study concluded that a 3mm margin with excision of early SCC lower lip is appropriate, if margins are controlled by systematic use of frozen-section analysis.

- The large, retrospective case series study by Griffiths (1999) found that 9 (7%) of excised BCCs were reported histologically as incompletely excised. Lateral margins alone were involved in 54 (55%), deep margins in 36 (36%) and both in 9 (9%). 74/99 (75%) tumours were re-excised and residual tumour was reported histologically in 40/74 (54%).

- A retrospective case series by Hsuan et al (2004) studied incomplete excision, recurrence and complications in 55 patients with nodular periocular BCCs. 10 (18%) excisions were incomplete, with no recurrences. The authors concluded that small margin excision of nodular adnexal BCCs with delayed repair is a safe and efficient method without resorting to Mohs labour intensive technique.

- A retrospective case series by Hussain and Earley (2003) found the incomplete excision rate for BCC to be 8%. The overall local recurrence rate was 5.5% - 5% following complete excision and 14% following incomplete excision. The nose was the commonest site for local recurrence after complete excision.

- A retrospective case series by Park, Strick, and Watson (1994) found the incomplete excision rate for BCC to be 11%. The overall local recurrence rate was 5.1%. 39% of lesions recurred locally if the tumour was incompletely excised compared with 1% for completely excised tumours.

- Timmons, Hessel, and Kranidhiotis (2002) studied incomplete excision rate in a retrospective case series of 557 BCCs from 440 patients and found 96.2% to be completely excised. However, excluding 9 “close to margin” excisions, this rate fell to 95%.

- The prospective case series study by Kumar et al (2002) studied the incidence of incompletely excised BCCs in 757 lesions from 600 patients. 34 lesions (4.5%) were incompletely excised and the commonest sites for incomplete excision of BCC were the eyebrow, followed by the post auricular area, the nose and the temple. Variables most likely to have affected the incidence of incomplete excision were found to be grade of surgeon (highest for SHOs and lowest for non-consultant career grades ($X^2(3)=8.41$; $p = 0.038$)), minimal excision margin and histological subtype (lowest in superficial BCC and highest in morphoeic BCC).

- An observational study by Robinson and Fisher (2000) found that the interval to local recurrence and to Mohs micrographic surgery following incomplete resection of BCC of the head was greater for men, patients older than 65 years, tumours on the nose or cheek, aggressive or fibrosing BCC, and those who underwent flap reconstruction (P =.001). The authors concluded that residual tumour should be treated immediately postoperatively.

- A prospective case series by Thomas, King, and Peat (2003) found that overall, complete excision was achieved for 98% of BCCs and 100% of SCCs. The authors recommend a 4-mm surgical margin as the optimal treatment for BCC/SCC suitable for excision in an outpatient facility.

# EVIDENCE TABLE 4.11

## *In patients with BCC or SCC, what are the rates of positive margins?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bisson *et al.* 2002) | To investigate excision margins. | Prospective case series. | 100 BCCs in 86 patients treated by conventional surgical excision.<br><br>**UK** | Comparison between the marked surgical margins and the margins observed on microscopy. | The mean observed surgical margin was 3.0 mm and the mean histological margin was 3.7 mm; 44% of the margins agreed to within 1 mm, 79% to within 2 mm and 92% to within 3 mm. There were four incomplete excisions, all at the lateral margin. There was agreement in the position of the closest margin in 69% of cases. The measured surgical excision margins correlated well with those assessed histologically, as did the position of the closest margin. | Given a 3 mm margin, 96% of lesions would have been excised completely. | 3 |
| (Chiller *et al.* 2000) | To determine whether curettage before excision of BCC and SCC improves margin clearance rates. | Retrospective cohort study. | 1983 BCCs and 849 SCCs<br>42% of BCCs and 34% of SCCs were curetted before excision.<br><br>**US** | Frequency of tumour margin involvement ("surgical failure"). | In BCC, risks for surgical failure included head and neck lesions (P<.001), lesions treated by physicians performing fewer than 51 procedures (P<.001), and invasive subtypes (P<.01). Factors associated with surgical failure in SCC included in situ disease (P=.01) and an older (77 vs. 74 years) patient population (P=.05).<br>In univariate analysis, curettage before excision decreased the surgical failure rate for BCC by 24% (P=.03) but did not decrease the rate for SCC (P=.8).<br>In multivariate analysis, curettage of BCC reduced surgical failure rates by 26% when the physician performed 50 | Authors describe this as a case-control study, but conducted as a cohort study – 2 groups used for comparison defined by intervention, not outcome.<br><br>Preoperative curettage decreases the frequency of positive margins in the management of BCC but not of SCC. | 2- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | skin cancer excisions or less during the study (odds ratio, 0.74; 95% confidence interval, 0.57-0.95;P=.02). | | |
| (de Visscher *et al.* 2002) | To evaluate the efficacy of 3mm margins of resection with surgical excision of SCC of the lower lip. | Prospective case series. | 72 patients with primary stage I (94.4%) or II SCC of the lower lip.<br><br>Full-thickness excision with 3mm margin. Intraoperative frozen section analysis used to confirm tumour-free margins Minimum follow-up 2 years.<br><br>**Holland** | Tumour recurrence. | Clinically determined margins were tumour-free in 89.9% on initial excision. False-positive rate associated with frozen-section analysis was 1.4%. Local recurrence found in 2 patients (2.8%). | Authors suggest that a 3mm margin with excision of early SCC lower lip is appropriate, if margins are controlled by systematic use of frozen-section analysis. | 3 |
| (Griffiths 1999) | To determine incomplete excision rate of BCCs and to determine residual tumour rate in re-excisions. | Retrospective case series. | 1392 BCCs arising in 1165 patients, excised under the care of one consultant in the 10 years from 1988 to 1997.<br><br>**UK** | Incomplete excision; residual tumour rate in re-excisions. | 9 (7%) were reported histologically as incompletely excised. Lateral margins alone were involved in 54 (55%), deep margins in 36 (36%) and both in 9 (9%). 74/99 (75%) were re-excised and residual tumour was reported histologically in 40/74 (54%). Peri-orbital lesions showed an overall incomplete excision rate of 13% (range 11-17%); however, only 4/16 of re-excisions in this area revealed residual tumour. | Authors suggest re-excision appears the appropriate course in almost all the anatomical areas studied although, with the exception of the inner canthus, periorbital lesions will have a low probability of residual tumour being identified. | 3 |
| (Hsuan *et al.* 2004) | To report the 5-year follow-up of patients with periocular BCCs treated with excision and delayed repair to allow for histological examination to confirm complete excision. | Retrospective case series. | 55 patients with nodular periocular BCCs 1994-1997 followed for 5-8 years, excised with 2 mm margins, and the repair delayed for 2 days, providing time for histological confirmation of complete excision with formal paraffin | Incomplete excisions; recurrence; complications. | 10 (18%) incomplete excisions; no recurrences. No complications between excision and repair, but 5 had significant complications post-repair (time-interval not given):<br>1 mild transient corneal ulcer secondary to a Hughes flap; 3 wound dehiscence (1 required further suturing); 1 trichiasis. | No information regarding size or histological subtype. Method of section – is this most appropriate for margin examination?<br><br>Patient preference for technique involving multiple operations not compared with preference for one session, as in Mohs. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | sections. Any incompletely excised tumours underwent further 2mm resection, which was facilitated by the undisturbed wound edges. Repair was again delayed until further histological examination had confirmed complete excision.<br><br>**UK** | | | No cost analysis to compare with Mohs. | |
| (Hussain & Earley 2003) | To quantify the incidence of incompletely excised BCCs and its association with the subsequent recurrence of the tumour and also to identify any variables that might affect it. | Retrospective case series. | 118 patients who had 126 BCCs excised Jan 95 - Dec 95 in a department of plastic surgery and followed for 3 years.<br><br>**Ireland** | incomplete excisions; recurrence rate. | Incomplete excision rate 10/126 (8%).<br>3 – residual tumour at deep margins<br>3 – residual tumour at lateral margins<br>3 – residual tumour at both margins<br>1 – not specified<br>Overall recurrence rate 5.5% - 5% following complete excision and 14% following incomplete excision. Lesion size not related to recurrence. Nose commonest site for recurrence after complete excision<br>6/7 of incompletely excised lesions, observed but not re-excised, did not recur during 3 year follow-up period. | | 3 |
| (Kumar *et al.* 2002) | To quantify the incidence of incompletely excised BCCs and examine possible variables associated with increased incidence. | Prospective multi-centre case series. | 757 lesions from 600 patients in a regional plastic surgery unit; a supraregional cancer hospital and a district general hospital.<br><br>**UK** | Incomplete excision rate. | 34 lesions (4.5%) were incompletely excised, the highest rate being in the supraregional cancer hospital (7.5%). Commonest site for incomplete excision was the eyebrow, followed by the post auricular area, the nose and the temple. Variables most likely to have affected the incidence of incomplete excision were found to be grade of surgeon (highest for SHOs and lowest for non-consultant career grades ($X^2(3)=8.41$; $p = 0.038$)), minimal excision margin and histological subtype (lowest in superficial BCC and highest in | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | morphoeic BCC). | | |
| (Park *et al.* 1994) | To assess the need for outpatient follow-up of patients who had primary BCCs excised by attempting to predict which tumours would recur. | Retrospective case series. | 192 patients with 215 BCCs 1986 – 1987.<br><br>**UK** | Incomplete excision rate; recurrence rate. | Incomplete excision rate 23/215 (11%).<br>5 – residual tumour at deep margins<br>14 – residual tumour at lateral margins<br>4 – residual tumour at both margins<br>Overall recurrence rate 11/215 (5.1%).<br><br>39% lesions recurred if tumour was incompletely excised cf. 1% if it had been completely excised. | Authors suggest that complete excision is key to surgical control and there is no need to follow-up patients routinely if the BCC has been completely excised. | 3 |
| (Robinson & Fisher 2000) | To determine whether there is an association among age or sex of patient, anatomic location, histologic type, or reconstructive procedures and the signs and symptoms of the recurrence, interval between incomplete resection and Mohs micrographic surgery, or extent of Mohs micrographic surgery resection. | Case series. | 994 patients with incompletely excised BCC of the head referred for Mohs micrographic surgery 1979-1999, prospectively recruited.<br><br>**US** | Interval to tumour recurrence, interval to Mohs micrographic surgery, and extent of Mohs micrographic surgery as determined by mean surface area resected, depth of resection, and number of tumour nests. | Interval to signs or symptoms of recurrence and to Mohs micrographic surgery from incomplete resection was greater for men, patients older than 65 years, when tumour on the nose or cheek, aggressive or fibrosing BCC, and those who underwent flap reconstruction (P =.001). The extent of Mohs micrographic surgery resection was greater for those with flap and split-thickness skin graft repairs. The number of tumour nests identified by Mohs micrographic surgery was significantly greater in those treated with split-thickness skin graft and flap (P =.001). | Authors conclude that because it is more difficult to control recurrent BCC, treating tumour remaining at the margin of resection in the immediate postoperative period could result in less extensive surgery. | 3 |
| (Telfer *et al.* 1999) | To provide evidence based guidelines on the treatment of patients with BCC on behalf of the British Association of Dermatologists. | Clinical guidelines. | Patients with BCC.<br><br>**UK** | Recommendations for clinical practice. | **Excisional surgery**<br>Surgical excision is a highly effective treatment for primary BCC.<br><br>For recurrent BCC, cure rates are inferior to those for primary lesions. Recurrent BCCs require wider peripheral surgical margins than primary lesions with or without standard (non-Mohs) frozen section control. Peripheral excision margins for recurrent BCC of 5-10 mm have been suggested.<br><br>The management of incompletely excised BCC remains controversial. Some evidence suggests that the total removal of some BCCs may not be | 91 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | necessary to effect cure and that up to two thirds of incompletely excised BCCs that are not re-treated do not recur. | | |
| (Thomas *et al.* 2003) | To determine the optimal excision margin for a non-melanotic skin cancer. | Prospective case series. | 91 BCCs and 37 SCCs excised by plastic surgeons.<br><br>**New Zealand** | Accuracy of clinical diagnosis; excision rate; shrinkage. Difference between surgical margin and pathologists' microscopic margin used to calculate which lesions would have been excised with an optimal 0.5mm microscopic margin, given a surgical margin of 1, 2, 3, or 4mm. | Mean surgical margin was 4.2 mm (3.2 mm adjusted for shrinkage), whereas the mean microscopic lateral margin was 3.4 mm.<br><br>Overall, complete excision was achieved for 98% BCCs and 100% SCCs.<br><br>Surgical margin of 4mm would have achieved an optimal excision beyond 1 microscopic high-power field in 96% BCCs and 97% SCCs (95% CI, 3.7 – 4.3mm). | Authors recommend a 4-mm surgical margin as the optimal treatment for skin lesions clinically diagnosed as BCC/SCC that are suitable for excision in an outpatient facility.<br><br>Well-demarcated lesions, such as a nodular BCC, may be excised with a 3-mm margin.<br><br>Evidence for recommendation about nodular-type does not arise from study. | 3 |
| (Timmons *et al.* 2002) | To determine incomplete excision rate. | Retrospective case series. | 557 BCCs from 440 patients in a Department of Plastic Surgery.<br><br>**UK** | Incomplete excisions. | 96.2% completely excised. However, if 9 "close to margin" excisions are excluded, rate falls to 95%. | | 3 |

**Mohs micrographic surgery**

**The questions**

*In patients with BCC how effective is Mohs micrographic surgery in preventing local recurrence?*

*In patients with BCC what is the impact on cosmesis of Mohs micrographic surgery?*

**The nature of the evidence**

Twelve studies were selected as follows:

- Three systematic reviews, one of good quality and two of poor quality
- One RCT of poor quality
- Two clinical guidelines of good quality
- Five observational studies of fair quality
- One expert review of fair quality

Four studies, including the clinical guidelines, originate from the UK. One study each is from the US and Canada. Three studies are from Holland and one study each is from Spain, France and Germany.

All studies are of patients with NMSC, of which seven report on patients with BCC.

**Summary of the supporting evidence for the recommendations**

**There is evidence consistently suggestive of a role for Mohs micrographic surgery in the treatment of patients with difficult NMSC lesions.**

**Evidence from three systematic reviews suggests that the rate of local recurrence of NMSC tumours following Mohs micrographic surgery (range 1.1% - 5.6%) appears to be lower than the rate following non**

**Mohs treatments (19.9%). This evidence and also evidence from UK evidence based clinical guidelines suggests that Mohs micrographic surgery should be used mainly for larger, aggressive and recurrent BCC tumours, located in high risk sites such as the face, including tumours with perineural invasion.**

**One RCT found no significant difference in recurrence rates between Mohs micrographic surgery and standard excision in patients treated for facial BCC, although the follow-up points were early, at 30 months for primary BCC and 18 months for recurrent BCC.**

**Evidence from UK clinical guidelines suggests that high cure rates are possible for SCC and BCC tumours that are otherwise difficult to treat. Observational study evidence is suggestive of high cure rates in difficult and especially, recurrent NMSC tumours, obtainable using Mohs micrographic surgery.**

**Observational study evidence suggests that factors associated with incomplete excision are multifocal positive skin margins, bony invasion, extension of tumour to other locations, and patients who are unable to tolerate further surgery.**

**Evidence from one expert review suggests that Mohs technique excises less uninvolved skin resulting in greater likelihood of simple closure, optimising the cosmetic outcome.**

- The case series study by Bentkover et al. (2002) found that the local recurrence rate of BCC following Mohs micrographic surgery with a cross-sectional frozen section histology technique was 2.1% at 5 years and concluded that the cross-sectional frozen-section recurrence rate compared favourably with rates for Mohs micrographic surgery.

- The case series study by Breuninger and Schaumburg-Lever (1988) found that Mohs micrographic surgery using tumour section fixed using routine methods was associated with low recurrence rates for different NMSC tumour types, including SCC and BCC.

- The prospective case series study by Julian and Bowers (1997) found that the local recurrence rate of BCC following Mohs micrographic surgery at 5 years follow-up was 3.8% and concluded that the technique is effective in both a teaching hospital and a district general hospital setting.

- The expert review by Lawrence (1999) concluded that less uninvolved skin is excised with Mohs micrographic surgery compared with conventional excision and that both completeness of excision and cosmetic outcome following treatment for BCC are more favourable with Mohs micrographic surgery.

- The large, retrospective case series study by Madani, Huilgol, and Carruthers (2000) found that of 10346 cases of Mohs micrographic surgery reviewed, incomplete excision following the technique was present in 15 cases (i.e. 0.14%). Sites of inadequate margin were nose, medial canthus, ear, scalp, and lower eyelid and reasons for termination of Mohs micrographic surgery were reported as ongoing, multifocal, positive skin margins, bony invasion, or extension of tumour to other locations.

- Evidence based clinical guidelines by Motley et al. (2003) recommend that surgical excision (including Mohs micrographic surgery) should be considered the first treatment of choice for patients with SCC and that the best cure rates for high risk SCC have been reported by Mohs micrographic surgery.

- The systematic review undertaken by Rowe, Carroll, and Day, Jr. (1989) found the 5-year recurrence rate of BCC following treatment by Mohs micrographic surgery to be 5.6%, compared to 19.9% following non-Mohs treatments. The review concluded that Mohs micrographic surgery is the treatment of choice for recurrent BCC.

- The systematic review undertaken by Sei et al. (2004) found that for NMSC tumours, Mohs micrographic surgery commonly induced lower

recurrence rates than conventional treatments and / or reduced surgical margins and concluded that Mohs micrographic surgery should be used mainly for larger, high risk, or recurrent BCCs located in surgically complex sites.

- The RCT by Smeets et al. (2004) compared wide excision with Mohs micrographic surgery as treatments for BCC on the face. There were no significant differences in recurrence rates at 30 months follow-up for primary tumours between randomised groups or at 18 months follow-up for recurrent tumours between groups. Aesthetic outcomes were similar following Mohs micrographic surgery or standard excision. The total operative costs of Mohs micrographic surgery were higher than those of standard excision.

- Evidence based clinical guidelines by Telfer, Colver, and Bowers (1999) recommend that Mohs micrographic surgery is indicated for BCC tumours at difficult sites (e.g. facial, ear), morphoeic, infiltrative and micro nodular subtypes of BCC, size > 2 cm and BCC tumours with perineural spread. The authors report that Mohs micrographic surgery offers highly accurate yet conservative removal of BCC with high cure rates for even the most difficult tumours.

- The systematic review by Thissen, Neumann, and Schouten (1999) found the recurrence rate for BCC following Mohs micrographic surgery to be 1.1% and recommended that the technique be used primarily for larger, morphea-type BCCs located in surgically complex areas.

- The case series study by Vuyk and Lohuis (2001) found the local recurrence rate for BCC treated with Mohs micrographic surgery to be zero, and 2% for SCC. The authors concluded that Mohs micrographic surgery has favourable cure rates.

# EVIDENCE TABLE 4.12

***In patients with BCC how effective is Mohs micrographic surgery in preventing local recurrence?***

***In patients with BCC what is the impact on cosmesis of Mohs micrographic surgery?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bentkover *et al.* 2002) | To compare a rapid, cross-sectional frozen-section technique with Mohs micrographic surgery. | Case series. | 557 head and neck BCCs excised over 10 years (dates not given).<br><br>**Spain** | Recurrence rates; tumour comparisons by size, location, and subtype. | Recurrence rate for the cross-sectional technique was 2.1% at 5 years. Recurrent tumours had an average diameter of 1.56 cm (vs. 1.04 cm for non-recurrent tumours). Recurrences were in the cheek (30%), nose (20%), temple (20%), forehead/brow (10%), conchal bowl (10%), and post auricular crease (10%). Recurrences were nodular cystic (40%), micro nodular (20%), multifocal (10%), and infiltrating (30%). | Authors conclude that cross-sectional frozen-section recurrence rates compare favourably with Mohs. | 3 |
| (Breuninger & Schaumburg-Lever 1988) | To determine the control of excisional margins by conventional histopathological techniques in the treatment of skin tumours. | Case series. | 1281 primary BCC; 178 recurrent BCC; 147 SCC; 4 dermatofibrosarcoma; 4 malignant fibrous histiocytoma; 21 malignant lentigo and 13 Bowen's disease.<br><br>Mean follow-up 4 years (2-7 years) for BCCs and 3 years (2-4 years) for other | Recurrence. | Intervention:<br>Routinely fixed tumour specimens or, under certain conditions, specimens fixed immediately in warm formalin are processed in the histology laboratory. Strips are then cut from the under-surface, edge, and cross-section of the remainder of the specimen and processed further by routine paraffin techniques until haematoxylin and eosin stained sections of the entire periphery and mid-section are available.<br><br>5 recurrences of fibrosing type BCC and | Extremely low recurrence rates over a relatively long follow-up period substantiate the effectiveness of the method. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | lesions.<br><br>**Germany** | | 1 of solid type BCC (4 primary, 2 recurrent) observed.<br><br>2 local recurrences of SCC observed. | | |
| (Julian & Bowers 1997) | To review use of Mohs micrographic surgery in the UK. | Prospective case series. | 72 BCCs in 67 patients in Nottingham 1981-1983 and 156 BCCs in 156 patients in Truro 1985-1995<br>Inclusion criteria: Large tumours, particularly in cosmetically sensitive area; tumours with no distinct margins e.g. morphoeic; tumours in an area of embryonic folds; persistently recurrent lesions.<br><br>**UK** | Recurrence rate. | Overall 5-year recurrence rate of 3.8%, representing 5 tumours, one primary and 4 previously treated. | Authors point out that recurrence rates are similar to those reported in US and that high cure rates in difficult and, especially, recurrent tumours are obtainable using Mohs in both a teaching and a district general hospital setting. | 3 |
| (Lawrence 1999) | To report on cosmetic outcome following Mohs micrographic surgery. | Expert review of two primary studies addressing cosmetic results following Mohs technique compared with predicted surgical margins. | Patients with BCC.<br><br>**UK** | Cosmetic outcome. | Re: cosmetic results:<br><br>Authors conclude that less uninvolved skin is excised with Mohs micrographic surgery compared with conventional excision and that completeness of excision and cosmetic outcome are better with Mohs technique due to its ability to excise tumours with asymmetrical spread. | | 4 |
| (Madani *et al.* 2000) | To examine the factors behind unplanned incomplete Mohs micrographic surgery and to identify means of avoiding and managing this situation when it arises. | Case series. | 10,346 cases of Mohs micrographic surgery.<br><br>**Canada** | Cases with positive margins at termination of surgery. | Incomplete Mohs excision was present in 15 cases (notes available for 14):<br><br>The tumours included 9 BCCs and 4 SCCs and 1 dermatofibrosarcoma protuberans. Sites involved were nose, medial canthus, ear, scalp, and lower eyelid. 12 cases dealt with unresectable disease, whereas 2 patients were | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | unable to tolerate further surgery.<br><br>Of the unresectable cases, Mohs micrographic surgery was terminated because of ongoing multifocal positive skin margins, bony invasion, or extension of tumour to other locations. Surgical defects were repaired, whereas residual disease was managed with a variety of methods.<br><br>Patients followed for 6 months – 13 years. Recurrences occurred in 2 cases (1 at 6 months, I at 5 years). | | |
| (Motley *et al.* 2003) | To provide evidence based guidelines on the treatment of patients with SCC on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons. | Evidence based clinical guidelines. | Patients with SCC.<br><br>**UK** | Recommendations for clinical practice. | Surgical excision (including Mohs) should be considered the first treatment of choice for patients with SCC.<br><br>**Mohs micrographic surgery**<br>The best cure rates for high risk SCC have been reported by Mohs micrographic surgery. | 82 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Rowe *et al.* 1989b) | To determine whether Mohs micrographic surgery has superior recurrence rates in the treatment of recurrent BCCs and thus should be the treatment of choice for these lesions. | Systematic review of all studies since 1945 reporting recurrence rates for treatment of recurrent BCCs (excision, radiotherapy, cryotherapy, curettage and electrodessication and Mohs). | 38 independent observations of recurrence rates; (17 excision; 6 radiotherapy, 6 curettage and electrodessication and 6 Mohs) divided into 2 groups; one reporting recurrence rates for 5 years follow-up and one reporting recurrence rates for less than 5 years follow-up.<br><br>**US** | Recurrence. | The 5-year recurrence rate for Mohs micrographic surgery is 5.6%. The recurrence rate for non-Mohs treatments is 19.9%. Individual recurrence rates for the non-Mohs treatments:<br>surgical excision 17.4%<br>curettage/electrodessication 40.0%<br>radiotherapy 9.8%<br><br>There are no studies reporting 5-year data for cryotherapy but the recurrence rate is 13.0% for cryotherapy when the follow-up period is less than five years. | All rejected papers listed and reasons for rejection given<br>Not able to appraise as an systematic review against given checklist – review pre-dates now accepted format for systematic reviews e.g. no search strategy given, no report of how methodological quality assessed.<br><br>Small numbers of studies for each treatment modality.<br><br>Authors conclude that Mohs micrographic surgery is the treatment of choice for recurrent BCC; if the patient is not a surgical candidate and the lesion is small, | 1- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | radiotherapy is an alternative that offers a better chance for cure than the other non-Mohs treatments; and curettage and electrodessication should not be used to treat recurrent BCCs. | |
| (Sei *et al.* 2004) | To systematically review literature for studies reporting on the role of Mohs micrographic surgery in the treatment of skin tumours. To show how well it is performed in France. | Systematic review. | 493 studies found (no details given, although stated that no RCTs found – systematic reviews and studies of lower quality).<br><br>**France** | Recurrence rates. | In tumours such as BCC or SCC, micro cystic adnexal carcinoma, dermatofibrosarcoma protuberans, and Merkel cell carcinoma, Mohs commonly induced lower recurrence rates than figures reported for conventional treatments and/or reduced surgical margins. | Authors conclude that Mohs should be used mainly for larger, morphea, micro nodular or infiltrative-type, or recurrent BCCs located in danger zones, but also (sometimes with a slightly modified procedure) in micro cystic adnexal carcinomas, dermatofibrosarcoma protuberans, Merkel cell carcinoma, and in aggressive forms of SCC.<br><br>ABSTRACT ONLY - FRENCH LANGUAGE.<br><br>Does not appear to discuss individual studies in any detail. Search limited to Medline and to English and French articles. No indication of how quality of included studies assessed ("with a quality grid").<br><br>Lack of detail of included studies. | 1- |
| (Smeets *et al.* 2004) | To compare wide excision versus Mohs micrographic surgery as treatments for BCC on the face. | RCT<br><br>Patients were randomised to either Mohs micrographic surgery or wide | 408 patients with primary facial BCC and 204 patients with recurrent facial BCC: mean ages 67.7 years and 67.9 years respectively. | Recurrence<br><br>Aesthetic outcome<br><br>Cost | **Recurrence rate**<br>Primary BCC:<br>At the 30 month follow-up point 3% of tumours in the SE group recurred compared to 2% of tumours in the Mohs micrographic surgery group (difference 1% [95% CI -2.5% to 3.7%], p = 0.724) | Both wide excision and Mohs micrographic surgery procedures were performed to a precise 3mm margin: Mohs micrographic surgery in practice, reportedly has smaller margins. | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | excision.<br><br>Analyses were performed separately for primary and recurrent BCC tumours.<br><br>Patients with primary BCC were followed up at 18 months and 30 months.<br><br>Patients with recurrent BCC were followed up at 18 months. | **Netherlands** | | i.e. no significant difference.<br><br>Recurrent BCC:<br>At the 18 month follow-up point No recurrences occurred in the Mohs micrographic surgery group compared to 3% in the SE group (difference 3.0% [95% CI -2.0% to 5.0%], p = 0.119) i.e. no significant difference.<br><br>**Aesthetic outcome**<br>Overall (for primary plus recurrent BCC), there was no difference in aesthetic outcome between Mohs micrographic surgery and wide excision treated tumours but primary tumours had better aesthetic outcome than recurrent tumours (p = 0.038, non ITT analysis).<br><br>**Cost**<br>Total operative costs of Mohs micrographic surgery were higher than those of SE (primary €405.79 vs. €216.86, recurrent €489.06 vs. €323.49; both p < 0.001). | Neither patients nor tumours were stratified within randomised groups for whether BCC was primary or recurrent.<br><br>Follow-up period acknowledged by authors as too short since 5 years is recognised as a better period in which to evaluate BCC recurrence.<br><br>Study has a mixture of ITT (for primary outcome: recurrence) and non ITT (for other outcomes) analyses. | |
| (Telfer *et al.* 1999) | To provide evidence based guidelines on the treatment of patients with BCC on behalf of the British Association of Dermatologists. | Clinical guidelines. | Patients with BCC.<br><br>**UK** | Recommendations for clinical practice. | Mohs micrographic surgery offers highly accurate yet conservative removal of BCC. It offers high cure rates for even the most difficult of BCCs together with the maximal preservation of normal tissues. The indications for using Mohs micrographic surgery include difficult sites (e.g. facial, ear), morphoeic, infiltrative and micro nodular subtypes, size > 2 cm and perineural spread. | 91 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Thissen *et al.* 1999) | To systematically review all prospective studies from 1970 to 1997 to compare the recurrence rates of the 5 most commonly used treatment modalities for | Systematic review of prospective studies of 50 patients (and tumours) or more with at least 5 years follow-up. | 18 case series were included (n = 9930).<br><br>**Holland** | Recurrence rate at follow-up of 5 years or more. | The authors state that the real recurrence rate will be somewhere between the estimated weighted strict and raw recurrence rates. Because most studies used different statistical methods for calculating their results, overall mean recurrence rates were not | Authors conclusion:<br>We surmise that Mohs micrographic surgery should be used mainly for larger, morphea-type BCCs located in danger zones. For smaller BCCs of the nodular and | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | BCC. The literature was also analysed for 2 investigational treatment modalities (immunotherapy with interferon alpha and/or beta or fluorouracil, and photodynamic therapy). | Studies were excluded if they reported on combinations of 2 or more therapies, reported on therapies other than those listed in the inclusion criteria, combined results of different types of cancer or reported results only for effectiveness as proved by excision and histopathology a few months later, or cosmetic results only. | | | calculated for every treatment modality.<br><br>Mohs micrographic surgery (3 studies, n=2660): Mean raw recurrence rate 0.8 (21/2660); Mean strict recurrence rate 1.1 (21/1989).<br><br>Surgical excision (3 studies, n = 1303): Raw recurrence rate was 1.4 in one study and 2.9 in another. Strict recurrence rate was 8.1 in one study. Mean cumulative 5 year rate (all 3 studies) was 5.3.<br><br>Cryosurgery (4 studies, n=796): Mean raw recurrence rate 3.0 (24/798); mean strict recurrence rate 4.3 (24/556); cumulative 5 year rate (3 studies) ranged from 0 to 16.5.<br><br>Curettage and desiccation (6 studies, n=4212): Raw recurrence rate (5 studies) ranged from 4.3 to 18.1; strict recurrence rate was given in one study as 8.5; cumulative 5 year rate ranged from 5.7 to 18.8.<br><br>Radiotherapy (1 study, n=862): Cumulative 5 year rate 7.4.<br><br>Immunotherapy (1 study, n=95): Raw recurrence rate 12.6, strict recurrence rate 21.4. | superficial types, surgical excision remains the first treatment of choice. Other treatment modalities can be used in patients in whom Surgery is contraindicated.<br><br>Comprehensive literature search and includes foreign language and grey literature. Data are appropriately combined, given the heterogeneity in statistical methods used between studies. Lack of individual study detail. No validity assessment of included studies – no weighting of less biased studies above more biased studies (although all prospective case series).<br><br>No details about numbers of reviewers or processes for data extraction.<br><br>Conflict of interest? Authors members of the reference centre for Mohs in the Netherlands.<br><br>Conclusions appear to be expert opinion rather than arising directly from the results. | |
| (Vuyk & Lohuis 2001) | To report effectiveness of Mohs micrographic surgery. | Case series. | 369 BCCs and 56 SCCs treated in an 8-year period using Mohs micrographic surgery.<br><br>Follow-up: Mean 33 months (3-99 | Recurrence. | No BCCs recurred. 1 SCC (2%) recurred a few months post-operatively.<br><br>Authors conclude that Mohs micrographic surgery has favourable cure rates. | Follow-up had range 3 months to 99 months (mean 33 months). | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | months).<br><br>**Holland** | | | | |

## Non-surgical therapies for patients with NMSC

### Topical therapy

### The question

*What is the role of topical therapy in the treatment of patients with skin cancer and pre-cancerous lesions?*

### The nature of the evidence

Eleven studies were identified as follows:

- One systematic review of good quality
- Three RCTs of good quality
- Five clinical guidelines/expert reviews, three of good quality and two of fair quality
- Two observational studies, one of fair quality and one of poor quality

Three studies are from the UK. Six studies are from the US , one study is from Canada and one study is from Germany. Applicability to the UK is reasonable.

Three studies are of patients with BCC. Seven studies are of patients with actinic keratosis and one study is of a single patient with Bowens disease.

### Summary of the supporting evidence for the recommendations

**Systematic review evidence suggests that in the treatment of BCC, cryotherapy has similar outcome with regard to local recurrence at one year to surgery, but poorer outcome compared to radiotherapy. The same level of evidence is suggestive of high success rates in superficial BCC for topical imiquimod, which can also produce useful response rates for nodular BCC. Evidence from a RCT on the role of imiquimod in treating superficial BCC is suggestive of no difference in clearance rates between a dose of five applications per week compared seven applications per week.**

**Fluorouracil is reported as a useful treatment for actinic keratoses in two expert reviews and clinical guidelines from the UK support fluorouracil as an effective treatment for low-risk, non invasive, extra facial BCC without follicular involvement.**

**Evidence from a single case report is suggestive of a role for imiquimod as a treatment option for Bowen's disease in patients where other treatment modalities such as surgery are contraindicated.**

- The systematic review of RCTs of treatments for BCC by Bath et al. (2004) found that cryotherapy, although convenient and less expensive than surgery, showed no significant difference in recurrences at one year, measured clinically, when compared to surgery, OR 0.23 (0.01 to 6.78). When radiotherapy was compared to cryotherapy there were significantly more recurrences at one year in the cryotherapy group, (OR 14.8, 95%CI, 3.17 to 69). A high success rate was found (87-88%) for imiquimod in the treatment of superficial BCC, as was a useful (76%) treatment response when treating nodular BCC.

- The expert review by the Consumers' Association (2002) reported that in the treatment of patients with actinic keratoses, fluorouracil can eradicate lesions with cure rates up to 93% whereas studies do not consistently support topical diclofenac as an effective treatment. Cryotherapy was reported as curing 99% of lesions but can lead to scarring and hypopigmentation.

- The RCT comparing imiquimod versus vehicle cream by Geisse et al. (2004) concluded that imiquimod is a safe and effective treatment for superficial BCC when compared with vehicle cream. The difference in clearance rates between a dose of 5 applications per week and seven applications per week was not significant.

- The single patient case report by Gutzmer et al. (2002) found that topical imiquimod brought about complete lesion regression in a patient with HPV 16 positive anogenital Bowen's disease and concluded that

imiquimod may be a treatment option for Bowen's disease, particularly in patients where other treatment modalities such as surgery are contraindicated.

- Clinical guidelines produced by Telfer, Colver, and Bowers (1999) recommended that topical 5-fluorouracil is an effective treatment low-risk, non invasive, extra facial BCC without follicular involvement. PDT and intraregional interferon were reported as investigational therapies.

- The expert review of treatments for patients with actinic keratoses undertaken by Tutrone et al. (2003) reported that topical 5-Fluorouracil can reduce lesions and that topical imiquimod can produce complete clearance of lesions, adding that both treatments are associated with side effects.

- The expert review by Gupta and Glover (2005) reported that 5% fluorouracil, applied topically twice a day, is an effective therapy for actinic keratosis with total clearance rates with range 43%-44.4%. Rates of adverse effects range from 80%-100%.

- The expert review by Jorizzo et al. (2004) reported that 5% and 0.5% fluorouracil concentrations have complete clearance rates of approximately 43% and that the side effect of skin irritation can be controlled by using a less frequent dose or by applying topical corticosteroids.

- The Randomised Controlled Trial by Rivers et al. (2002) compared topical 3.0% diclofenac in 2.5% hyaluronan gel with 2.5% hyaluronan gel alone as placebo, in the treatment of patients with actinic keratosis. After 60 days of twice daily application (assessed 30 days post treatment), significantly greater proportions of patients in the active treatment group had lesion improvement as determined by both objective and subjective scoring measurements, than those in the placebo group.

- The Randomised Controlled Trial by Wolf et al. (2001) compared topical 3.0% diclofenac in 2.5% hyaluronan gel with 2.5% hyaluronan gel alone as placebo, in the treatment of patients with actinic keratosis. After 90 days of treatment (assessed 30 days post treatment) significantly greater proportions of patients in the active treatment group had lesion improvement as determined by both objective and subjective scoring measurements, than those in the placebo group.

- The case series study by Nelson et al. (2004) of 67 patients diagnosed with five or more actinic keratosis found that topical treatment with 3% diclofenac for 90 days resulted in lesion improvement at the assessment point at 30 days post treatment, as measured by objective and subjective scoring measurements.

# EVIDENCE TABLE 4.13

***What is the role of topical therapy in the treatment of patients with skin cancer and pre-cancerous lesions?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bath *et al.* 2004) | To assess the effects of treatments for BCC. | Systematic review of RCTs. | Patients with BCC.<br><br>**Review undertaken in the UK** | The primary outcome measure was recurrence at 3- 5 years, measured clinically. The secondary outcome included early treatment failure within 6 months, measured histologically. Adverse effect of treatment was evaluated by reviewing aesthetic appearance (to patient and blinded observer) and pain during and after treatment. | 19 studies (13 published and 6 abstracts) were identified which include 7 broad therapeutic categories.<br><br>Only one RCT of surgery versus radiotherapy had primary outcome data at four years, which showed that there were significantly more persistent tumours and recurrences, measured histologically, in the radiotherapy group as compared to the surgery group, which translates to an odds ratio of 0.09 (95%CI, 0.01 to 0.67) in favour of surgery.<br><br>Cryotherapy, although convenient and less expensive than surgery, showed no significant difference in recurrences at one year, measured clinically, when compared to surgery, OR 0.23 (0.01 to 6.78).<br><br>However when radiotherapy was compared to cryotherapy there were significantly more recurrences at one year, measured histologically, in the cryotherapy group, this translates to an odds ratio of 14.80 (95%CI, 3.17 to 69) in favour of radiotherapy. | Inclusion criteria were adults with one or more histologically proven, primary BCC.<br>Study selection and assessment of methodological quality were carried out by two independent reviewers. | 1 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Preliminary studies suggest a high success rate (87-88%) for imiquimod in the treatment of superficial BCC using a once-daily regimen for 6 weeks and a useful (76%) treatment response when treating nodular BCC for 12 weeks, when measured histologically. However this cream has not been compared to surgery.<br><br>Authors conclude: There has been very little good quality research on efficacy of the treatment modalities used. Most of the trials have looked only at BCCs in low risk areas. Surgery and radiotherapy appear to be the most effective treatments with surgery showing the lowest failure rates. Other treatments might have some use but few have been compared to surgery. Imiquimod emerged as a possible new treatment although it has not been compared to surgery or any other modality. | | |
| (Consumers' Association 2002) | To review the prevention and treatment of solar keratoses. | Expert review (29 references). | Patients with actinic keratoses.<br><br>**UK** | Reports findings of primary studies. | There is no consensus among experts whether to obliterate all AK lesions since only a minority show malignant transformation. Topical treatments include:<br><br>Fluorouracil: This has been found to eradicate lesions with cure rates up to 93% reported when applied for 3-4 weeks. Side effects include a painful, burning inflammatory response which may respond to topical steroids and which is exacerbated by sunlight.<br><br>Diclofenac: Some studies report that diclofenac in hyaluronic acid can be more effective in resolving lesions than vehicle alone when applied over 30-90 | | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | days, but this finding is not consistent.<br>Other treatments:<br><br>Cryotherapy has been found to cure 99% of lesions but can lead to scarring, hypopigmentation and infection. | | |
| (Geisse *et al.* 2004). | To evaluate the efficacy and safety of imiquimod 5% cream compared with vehicle for treating superficial BCC (sBCC). | RCT comparing imiquimod versus vehicle cream once daily. | Patients with superficial BCC.<br><br>**US** | Clearance rates by histological and clinical examination. | Composite clearance rates (combined clinical and histological assessments) for the 5 and 7 applications/week imiquimod groups were 75% and 73%, respectively.<br><br>Histological clearance rates for the 5 and 7applications/week imiquimod groups were 82% and 79%, respectively.<br><br>Increasing severity of erythema, erosion, and scabbing/crusting was associated with higher clearance rates.<br><br>Authors conclude that imiquimod appears to be safe and effective for the treatment of sBCC when compared with vehicle cream. The difference in clearance rates between the two imiquimod dosing groups was not significant. The 5 applications/week regimen is recommended. | Trial run as two smaller trials: one of 5 applications per week and one of 7 per week for 6 weeks . Data from both studies pooled for analysis. Double-blinding applied. | 1 + |
| (Gupta & Glover 2005) | To provide an overview of literature on the role of fluorouracil formulations in the treatment of patients with actinic keratosis. | Expert review. | Patients with actinic keratosis.<br><br>**US** | Clearance rates and adverse effects as reported in primary studies. | **5% fluorouracil**<br>Studies report 5% fluorouracil cream, ointment and solution, applied twice a day, to be effective therapies for actinic keratosis, associated with mild or moderate irritation, erythema, burning and dryness. Rates of adverse effects range from 80-100%. Adverse effects can be very visible on facial areas. Treatment is associated with total clearance rates of 43%-44.4%. Responses can be achieved in approximately two weeks. | Search strategy described. Randomised and non randomised studies cited.<br><br>Results tabulated, but high heterogeneity present. | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Treatment of lesions on the hands and forearms is reported as less effective than those on the scalp or face, with a 70% reduction in lesions reported.<br><br>**0.5% fluorouracil**<br>Randomised studies have found no significant difference in reduction of number of lesions and also clearance rates, between 0.5% preparations used with a microsphere delivery system, and 5% preparations.<br><br>0.5% fluorouracil applied once a day can achieve reduction of the number of lesions in 88.8-91.7% of patients at 4 weeks and total clearance in 47.5-57.8% of patients at 4 weeks.<br><br>Author reports that 0.5% fluorouracil appears to be as effective as 5% fluorouracil in the treatment of actinic keratosis. | | |
| (Gutzmer *et al.* 2002) | To report on the treatment of a single patient with anogenital Bowen's disease. | Case report. | 1 patient with extensive HPV 16 positive anogenital Bowen's disease.<br><br>**Germany** | Clinical regression of lesions. | After 5 months of local treatment with imiquimod, the lesions completely regressed clinically and histologically, and HPV 16 DNA was no longer detectable.<br><br>Moreover, DNA image cytometry revealed DNA aneuploidy (an indicator of prospective malignancy) in pre-treatment samples but not in post-treatment samples.<br><br>Therefore, imiquimod might be a treatment option for Bowen's disease, particularly in patients where other treatment modalities such as surgery are contraindicated. | n = 1. | 3 - |
| (Jorizzo *et al.* 2004) | To describe treatment strategies for actinic keratosis. | Expert review. | Patients with actinic keratosis. | As reported in primary studies: commonly lesion | **Fluorouracil**:<br>The 5% and 0.5% concentrations are the most widely used fluorouracil | 66 references. No evidence of systematic literature search. | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | **US** | clearance rates. | products. Both agents have complete clearance rates of approximately 43%. Fluorouracil related skin irritation can be controlled by using a less frequent dose or by applying topical corticosteroids.<br><br>**Imiquimod**:<br>5% Imiquimod has been associated with clearance rates of 45.1 - 100%. Localised skin reactions are the most common reactions.<br><br>**Diclofenac sodium 5%**<br>5% diclofenac is an alternative to fluorouracil and has been found to be favourable to vehicle cream in randomised studies, with up to 100% in some patients. Diclofenac is reportedly well tolerated. | | |
| (Nelson *et al.* 2004) | To assess the efficacy and tolerability of 3.0% diclofenac sodium gel in the treatment of patients with actinic keratosis. | Case series.<br><br>Patients were treated with topical 3% diclofenac for 90 days with assessment for outcomes at 30 days follow-up, post treatment. | 67 patients diagnosed with five or more actinic keratosis lesions contained in 1 to 3 blocks (5 $cm^2$) on the forehead, central face, or scalp.<br><br>Mean age was 68.2, range 48-100 years.<br><br>**US** | Proportion of patients with 75% lesion clearance rate at day 90 and at day 120 (follow-up visit). This was based upon target lesion number score (TLNS) at baseline.<br><br>Cumulative lesion number score (CLNS) and investigator Global Improvement Index (IGII). | At Day 90 of treatment, 78% of patients (95% CI 68% to 87%) had 75% or more lesion clearance based upon TLNS. This measure was 85% (95% CI 77% to 94%) at day 120 (follow-up).<br><br>Improvement was also demonstrated by the proportion of patients in whom there was 100% lesion clearance based on TLNS: At Day 90 of treatment: 41% (95% CI 29% to 52%) ; Day 120 (follow-up): 58% (95% CI 46% to 70%).<br><br>Similar improvements were shown in CLNS. At day 90 69% (95% CI 58% to 80%) had 75% lesion clearance. At day 120 (follow-up) 72% (95% CI 61% to 82%) had 75% lesion clearance.<br><br>Measurement of IGII confirmed the efficacy of 3.0% diclofenac gel in the clearance of actinic keratosis lesions: Investigators considered the lesions to be significantly improved for 45% and | 'Open label study' i.e. patients and investigators were aware of therapy applied.<br><br>Of the 76 patients who entered the study, 67 (88%) patients completed the study.<br><br>At baseline, patients had mild or moderate actinic keratosis, by the baseline severity index (BSI) score.<br><br>Statistical significance of differences not assessed. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | completely improved for 27% of patients at day 90. These figures were 42% and 42% respectively at day 120.<br><br>A total of 39 patients (51%) experienced at least 1 adverse event considered to be related to 3.0% diclofenac sodium gel during the study. Dry skin and rash at the application site were the most commonly reported adverse events, and most of these adverse events were mild or moderate in severity. Authors conclude that topical application of 3.0% diclofenac sodium gel provides a safe and effective approach for the treatment of actinic keratosis. | | |
| (Rivers *et al.* 2002) | To evaluate the efficacy and safety of 3.0% diclofenac in 2.5% hyaluronan gel as a treatment for actinic keratosis. | RCT<br><br>**Intervention:** Patients randomised into the active treatment groups A30 (n = 49) and A60 (n = 48) received topical treatment with 3.0% diclofenac in 2.5% hyaluronan gel 0.5 g twice daily for 30 or 60 days, respectively.<br><br>**Control:** Patients in the placebo (vehicle gel) groups V30 (n = 49) and V60 (n = 49) received topical treatment with 2.5% hyaluronan gel 0.5 g twice daily for 30 or 60 days, respectively. | 195 Caucasian patients with at least five actinic keratoses in 3 or less 5cm$^2$ areas. Women who may become pregnant during the study were excluded. 73% of patients were male.<br><br>**Canada** | Treatment efficacy was assessed by target (i.e. absolute) and cumulative lesion number scores (TLNS and CLNS, respectively) and lesion total thickness score (TTS). Investigator and patient global improvement indices (IGII and PGII) were also used to rate overall improvement. | Compared with placebo, significantly more patients given active treatment for 60 days had TLNS = 0 (33% vs. 10%, p < 0..05; an improvement of 64% compared with 34% with placebo), CLNS = 0 (31% vs. 8%, p < 0..05; an improvement of 54% compared with 23% with placebo) and TTS = 0 (25% vs. 6%, p < 0..05; an improvement of 59% compared with 31% with placebo).<br><br>The IGII and PGII scores were also significantly better when active treatment was compared with placebo (p < 0.05).<br><br>Both treatments were generally well tolerated and the incidence of the most common adverse events was similar between groups.<br><br>Authors conclude that treatment with 3.0% diclofenac in 2.5% hyaluronan gel was effective when used for 60 days and was well tolerated in patients with actinic keratosis. | Multi-centre, placebo controlled, double blind RCT.<br><br>Study compared two dose schedules as well as treatment versus placebo.<br><br>Possible bias may favour treatment: since some non participants were ineligible due to refusal to cease other treatment or cosmesis prior to the study.<br><br>Follow-up assessment was made at 30 days post treatment in all groups. | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Telfer *et al.* 1999) | To provide evidence based guidelines on the treatment of patients with BCC on behalf of the British Association of Dermatologists. | Clinical guidelines. | Patients with BCC.<br><br>**UK** | Recommendations for clinical practice. | **Topical therapy**<br>Topical therapy mainly involves topical 5-fluorouracil (5FU). Treatment is especially useful for low-risk, extra facial BCC but it cannot be expected to eradicate invasive BCC or lesions with follicular involvement. Topical 5FU therapy can be particularly helpful in the management of multiple superficial BCCs on the trunk and lower limbs.<br><br>**Interferon**<br>Treatment of BCC with intralesional interferon alpha is still essentially investigational and long term cure rates are not yet available. | 91 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Tutrone *et al.* 2003) | To review evidence on topical 5-fluorouracil and imiquimod in the treatment of actinic keratoses. | Expert review (31 references). | Patients with actinic keratoses.<br><br>**US** | Regression of lesions and side effects of treatment as reported by primary studies. | Topical 5-Fluorouracil can reduce lesions when applied at 0.5%. Common side effects are mild to moderate facial irritation, erythema, dryness and burning. Imiquimod 5% cream can produce complete clearance of lesions, but side effects are common, including erythema, scabbing, pruritus and flaking. | | 4 + |
| (Wolf, Jr. *et al.* 2001) | To compare the efficacy and safety of 3% diclofenac in 2.5% hyaluronan gel with placebo 2.5% hyaluronan gel alone, in the treatment of AK. | RCT<br><br>**Intervention (n=58)**: 3% diclofenac gel in 2.5% hyaluronan gel twice daily for 90 days.<br><br>**Control (n=59)**: inactive gel vehicle (hyaluronan) as placebo for 90 days. | 96 patients with a diagnosis of five or more AK lesions contained in one to three 5 $cm^2$ areas of skin.<br><br>**US** | Target Lesion Number Score (TLNS), Cumulative Lesion Number Score (CLNS), and Global Improvement Indices rated separately by both the investigator (IGII) and patient (PGII).<br><br>Outcomes were proportion of patients with: | A significantly higher proportion of patients who received active treatment had a TLNS = 0 compared to the placebo group (50% vs. 20%; $p < 0.001$).<br><br>There was also a significant difference between the two groups in CLNS, with 47% of patients in the active treatment group having a CLNS = 0 compared with only 19% in the placebo group ($p < 0.001$).<br><br>The proportion of patients with an IGII score of 4 (completely improved) at follow-up was 47% in the active treatment group compared with only | Results were obtained at a single follow-up point: 30 days after the end of treatment.<br><br>Of 120 patients enrolled to the study, 96 patients completed the study. 22 patients withdrew: 14 from the intervention group and 8 from the placebo group.<br><br>Study was double-blinded. | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | TLNS=0;<br>CLNS=0<br>IGII=4<br>PGII=4. | 19% in the placebo group (p < 0..001); for PGII these values were 41% vs. 17%, p < 0.001.<br><br>Both treatments were well tolerated, with most adverse events related to the skin. Authors conclude that topical 3% diclofenac in 2.5% hyaluronan gel is effective and well tolerated for the treatment of AK. | | |

## Photodynamic therapy

### The question

*What is the usefulness of Photodynamic Therapy (PDT) in the treatment of NMSC?*

### The nature of the evidence

Seven studies were identified as follows:

- Three RCTs of poor quality
- Two clinical guidelines, of good quality
- One observational study of poor quality
- One expert review of good quality

Three studies originate from the UK. Two studies are from the US, one is a European collaboration and one study is from Switzerland. Applicability to the UK is limited, due to the lack of primary studies from the UK.

Three studies address patients with BCC and four studies consider patients with NMSC and premalignant lesions.

### Summary of the supporting evidence for the recommendations

**Evidence from RCTs supports the use of PDT with methyl aminolaevulinate (MAL) in the treatment of actinic keratoses and BCC. In BCC cosmetic outcome is better following PDT than surgery, but with higher recurrence rate. However PDT is also associated with side effects and RCTs of PDT often have the drawback of only analysing patients who complete the treatment regimen.**

**Clinical guideline evidence from the UK suggests that PDT is an effective treatment for patients with actinic keratoses on the face and scalp, Bowen's disease and superficial BCC, but is less suitable for nodular BCCs and SCCs. Expert review evidence suggests that PDT has**

**higher rates of local recurrence of BCC compared to both surgical excision and Mohs micrographic surgery, and should be reserved for only those patients who cannot undergo surgical therapy for BCC and SCC.**

**Evidence from one observational study suggests that in superficial BCC, tumour thickness is predictive of response to PDT.**

- The RCT by Dragieva et al. (2004) compared topical PDT with methyl aminolaevulinate (MAL) with placebo in the treatment of patients with actinic keratoses after organ transplant. The overall lesion complete response rate was 90% in the active treatment group and 0% in the placebo group ($p = 0.0003$).

- The expert review by Marmur, Schmults, and Goldberg (2004) reported that PDT is capable of achieving clearance rates comparable to radiotherapy for BCC, but for BCC, remains inferior in terms of local recurrence, to surgical excision and Mohs micrographic surgery. The use of PDT is restricted in treating patients with SCC due to the risk of metastatic disease. The study concluded that PDT should be reserved for only those patients who cannot undergo surgical therapy for BCC and SCC.

- Clinical guidelines produced by Morton et al. (2002) report that whilst a consensus of technique is yet to be established, topical PDT is an effective treatment for patients with actinic keratoses on the face and scalp, Bowen's disease (with results comparable to Fluorouracil or cryotherapy) and superficial BCCs (with results comparable to cryotherapy). PDT is however a relatively poor option for both nodular BCCs and SCCs.

- The prospective case series study by Morton et al. (1998) found PDT to be an effective treatment for thin, superficial BCCs with excellent cosmetic outcome, where tumour thickness predicted response.

- The RCT by Pariser, Divers, and Nassar (1999) compared PDT using MAL cream with PDT using placebo cream in the treatment of patients with actinic keratosis. Complete lesion response rate was higher after MAL PDT than after placebo PDT and an excellent or good cosmetic outcome was reported in more than 90% of patients treated with MAL PDT.

- The RCT by Rhodes et al. (2004) compared the use of topical PDT using methyl aminolevulinate with standard excision surgery in 101 patients with nodular BCC. The study found that PDT had superior cosmetic outcome than surgery, whereas BCC recurrence assessed at 24 months after treatment was higher after PDT compared to surgery.

- Clinical guidelines produced by Telfer, Colver, and Bowers (1999) report that PDT is not widely used in the UK.

# EVIDENCE TABLE 4.14

## *What is the usefulness of Photodynamic Therapy (PDT) in the treatment of NMSC?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Dragieva *et al.* 2004) | To evaluate the efficacy and tolerability of topical PDT with methyl aminolaevulinate (MAL) versus placebo in the treatment of actinic keratoses in transplant recipients. | RCT<br><br>Intervention (n=17): 1mm thick topical application of MAL for 3 hours followed by 75 $Jcm^{-2}$ of visible light at 80$mWcm^{-2}$ with a spectrum of 600-730nm.<br><br>Control (n=17): As above, but with placebo cream.<br><br>Two treatments were given, one week apart. | 17 transplant patients (13 kidney, 4 heart) with a total of 129 actinic keratosis lesions.<br><br>Mean age 61 (range 44-76) years.<br><br>**Switzerland** | Proportion of lesion areas with complete response (CR), partial response (PR) or no response (NR), evaluated at weeks 4, 8 and 16 after treatment. | At 16 weeks follow up, CR was seen in 13 (95% CI 9-16) of 17 patients treated with MAL with a PR in a further 3 and NR in one patient.<br><br>NR was seen in all placebo-treated areas.<br><br>The overall lesion complete response rate was 56 of 62 for treatment of fields with PDT with MAL and 0 of 67 for treatment of fields with PDT with placebo (p = 0.0003).<br><br>Adverse events, such as erythema, oedema and crust formation, were mild to moderate, and treatment was well tolerated by all patients. | Randomisation was by treatment field. There were 2 treatment fields in each of 17 patients, but it is not clear whether each patient received MAL and placebo, or just one or the other.<br><br>Trial was double blinded.<br><br>Small sample size, but adequate power calculation performed. | 1 - |
| (Marmur *et al.* 2004) | To review literature pertaining to the use of light-emitting technologies and Photodynamic Therapy (PDT) for the treatment of BCC, SCC, and Actinic Keratosis (AK). | Expert review (28 references). | Numerous primary study populations of patients with BCC, Actinic Keratoses, SCC in situ and SCC.<br><br>**Review undertaken in the US** | Clearance rates from primary studies, noting periods of follow-up. | A total of 20 papers were included for review (10 for BCC, 4 for AK, and 6 for SCC). Follow-up for these patients ranged from 1 to 36 months.<br><br>Clearance rates were reported up to 100% for superficial BCCs, AKs, and SCC in situ, and lower (8%) for more invasive SCC. | A National Library of Medicine PubMed Internet search of English-language journals was performed using the terms laser, PDT, BCC, SCC, and AK. The search encompassed all English-language clinical trials on human subjects from the mid-1960s to the present using | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Recurrence rates ranged from to 0% to 31% for superficial BCCs, 16% to 31% for AKs, 0% to 52% for SCC in situ, and 82% for invasive SCC.<br><br>Precise PDT and laser clearance and recurrence rates for nodular BCC and SCC treated with laser and PDT are not yet known.<br><br>From the available data, it appears that PDT may be capable of achieving clearance rates comparable to radiotherapy for BCC. However, with current technology, PDT treatment of BCC remains inferior to surgical excision and Mohs micrographic surgery, for which recurrence rates have been reported to be less than 10%.<br><br>The reported clearance rates currently limit the usefulness of PDT and laser therapy. However, multiple treatments and the use of penetration enhancers may significantly increase the efficacy of 5-aminolevulinic acid-PDT.<br><br>With regard to SCCs, the risk of metastatic disease restricts the use of laser and PDT.<br><br>Studies are currently underway with new light sources, photo sensitizers, and various therapeutic regimens. At this time, because the reported recurrence rates are significantly higher than those achieved with standard therapies, laser and PDT should be reserved for only those patients who cannot undergo surgical therapy for BCC and SCC. | laser and light source therapy and/or topical aminolevulinic acid. Articles were excluded if they contained fewer than 10 patients, had a follow-up time of less than 1 month, used intravenous photo sensitizers, or were review articles. | |
| (Morton *et al.* 2002) | To provide clinical | Clinical guidelines | Numerous primary | Clearance rates | 5-Aminolaevulinic acid (ALA) is the | Appraised with AGREE | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | guidelines on the role of PDT in the treatment of NMSCs. | (119 references). | study populations of patients with BCC, Actinic Keratoses, SCC in situ and SCC.<br><br>**UK** | from primary studies, short and longer term side effects. | main agent used in PDT. Accurate dosimetry in PDT is complicated by multiple variables in drug formulation, delivery and duration of application, in addition to light-specific parameters and consensus of technique is yet to be established.<br><br>The carcinogenic risk of ALA-PDT appears to be low.<br><br>Current evidence indicates topical PDT to be effective in actinic keratoses on the face and scalp, Bowen's disease (with results comparable to Fluorouracil or cryotherapy) and superficial BCCs (with results comparable to cryotherapy).<br><br>PDT may prove advantageous where size, site or number of lesions limits the efficacy and/or acceptability of conventional therapies.<br><br>Topical ALA-PDT alone is a relatively poor option for both nodular BCCs and SCCs.<br><br>Side effects include short term pain, usually tolerated without analgesia, erythema and oedema. Chronic and carcinogenic effects are rare. Experience of the modality in other skin diseases remains limited; areas where there is potential benefit include viral warts, acne, psoriasis and cutaneous T-cell lymphoma. | checklist. | |
| (Morton *et al.* 1998) | To assess the effect of tumour thickness and duration of PDT on response in the treatment of BCC. | Prospective case series, with comparison of group treated with 4 hrs PFT vs. group treated by 6 hrs | 53 patients with histologically proven superficial BCC aged 29-96.<br><br>**UK** | Clinical response by monthly intervals. | Complete response rate was higher in the 6 hour group than the 4 hour group ($p = 0.005$). The sizes of lesions treated were similar in each group: median 2.88 cm2 in 4 hour group and 2.35 cm2 in 6 hour group. Tumour thickness was a | | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | PDT. | | | predictor of response in the 4 hour group ($p < 0.0001$) and response rate was 100% in the 6 hour group. Severe pain requiring analgesia was experienced in the two largest lesions treated, otherwise pain was mild or absent. Cosmetic outcome was excellent in all tumours. Authors conclude that PDT is an effective treatment for thin, superficial BCCs, where tumour thickness appears to predict response. | | |
| (Pariser *et al.* 1999) | To compare PDT using 160 mg/g Methyl aminolevulinate (MAL) cream with PDT using placebo cream in the treatment of actinic keratoses. | RCT<br><br>Intervention (n = 42):<br>MAL PDT.<br><br>Control (n = 38):<br>Placebo PDT.<br><br>After application of the cream under occlusion for 3 hours, the lesions were illuminated by noncoherent red light: 570-670 nm, light dose 75 $Jcm^{-2}$.<br><br>Treatment was repeated after 1 week and response was assessed 3 months later. | 80 patients with actinic keratosis lesions (70 men, 10 women), mean age 65 (range 31-84) years.<br><br>**US** | Proportion of patients who experienced a complete response to treatment. | Complete lesion response rate was higher after MAL PDT than placebo PDT: 32/39 (89%) versus 8/38 (38%) respectively; estimated difference: -61%, 95% CI -81% to -41%) ($p = 0.001$) per protocol analysis.<br><br>The lesion response rate was higher in the MAL PDT group than the placebo PDT group: 209/236 (89%) versus 92/241 (38%).<br><br>An excellent or good cosmetic outcome was reported in more than 90% of patients treated with MAL PDT.<br><br>90% of patients in the MAL PDT group reported any adverse event, compared to 58% of patients in the placebo PDT group. Adverse events included burning, pain, oedema, crusting and blistering and were mild in the majority of patients in both groups.<br><br>Authors conclude that PDT using topical MAL is a safe and effective treatment for actinic keratoses with excellent cosmetic outcome. | Per protocol analysis is not as robust as intention-to-treat analysis. | 1 - |
| (Rhodes *et al.* 2004) | To compare topical PDT, with the use of the | RCT | 101 adults with previously untreated | Clinically assessed lesion clearance at | Complete response rates did not differ significantly between groups (51/52 | Data from 97 patients (105 lesions) were included in the | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | sensitizer methyl aminolevulinate (MAL), and standard excision surgery in nodular BCC. | Patients received PDT with MAL (n = 52) or surgery (n = 49).<br><br>The PDT was given twice, 7 days apart, with MAL cream (160 mg/g) and 75 $Jcm^{-2}$ red light (570-670 nm). | nodular BCC.<br><br>**Multi-centre, European** | 3 months after treatment.<br><br>Sustained response rate at 12 months after treatment.<br><br>Cosmetic outcome at 3, 12 and 24 months.<br><br>Lesion recurrence at 24 months. | [98%] lesions with surgery vs. 48/53 [91%] lesions with PDT (difference 4.8% (95% CI -3.4% to 13.0%; p = 0.25).<br><br>At 12 months, tumour-free rates were 50 (96%) of 52 lesions with surgery vs. 44 (83%) of 53 with PDT (p = 0.15).<br><br>More patients treated with PDT than surgery had an 'excellent' or 'good' cosmetic outcome at all follow-up points (significantly so at 12 and 24 months on patient assessment, p < 0.05, and at 3, 12, and 24 months on investigator evaluation, p < 0.001).<br><br>At 24 months, 5 lesions that had initially cleared with PDT had recurred, compared with 1 after surgery.<br><br>More patients treated with PDT reported adverse events compared to those treated with surgery: 27/52 (52%) and 14/49 (29%) respectively, p = 0.03, including burning, pain and erythema.<br><br>Authors conclude that PDT is an effective treatment for nodular BCC, and while there is a trend for higher recurrence with this modality, it conveys the advantage over surgery of better cosmesis. | 3-month per-protocol analysis i.e. not as robust as an intention to treat analysis.<br><br>Study excluded patients with ≥10 lesions, large lesions and pigmented or morpheaform lesions.<br><br>Randomisation was stratified for treatment centre. | |
| (Telfer *et al.* 1999) | To provide evidence based guidelines on the treatment of patients with BCC on behalf of the British Association of Dermatologists. | Clinical guidelines. | Patients with BCC.<br><br>**UK** | Recommendations for clinical practice. | The use of PDT in BCC remains investigational and is not widely used in the UK. | 91 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |

## Destructive therapies for patients with NMSC

### The question

*What destructive therapies are available for the treatment of patients with NMSC or premalignant lesions?*

### The nature of the evidence

The role of $CO_2$ laser therapy is further discussed in the treatment of patients with Gorlin's syndrome in Chapter six, 'Management of special groups of patients with skin cancer'.

Three UK clinical guidelines, of good quality were identified, and applicability to the UK is therefore good. The guidelines relate to patients with Bowen's disease, patients with SCC and patients with BCC.

### Summary of the supporting evidence for the recommendations

**Evidence from UK clinical guidelines supports the use of cryotherapy in the treatment of patients with Bowen's disease, SCC (where good short term cure rates are achievable) and primary BCC. Curettage and electrodessication is cautiously supported in treating patients with Bowen's disease, patients with small, well differentiated and slow growing SCC and low risk, primary BCC.**

- Clinical guidelines for the treatment of patients with Bowen's disease produced on behalf of the British Association of Dermatologists by Cox, Eedy, and Morton (1999) recommended that cryotherapy appears to have a good success rate with local recurrences less than 10% at 12 months, but noted that discomfort may limit treatment of multiple lesions. The recurrence rate following curettage with cautery / electrocautery was reported with range zero to 20%, with a failure rate of up to 73% and this treatment was supported by low quality primary studies.

- Clinical guidelines for the treatment of patients with SCC were produced by Motley et al. (2003) on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons. Curettage and cautery were reported with excellent cure rates in small, (<1 cm) well differentiated, primary, slow growing SCC tumours and cryosurgery was reported as giving good short term cure rates and was recommended for use in specialist centres by experienced practitioners.

- Clinical guidelines for the treatment of patients with BCC on behalf of the British Association of Dermatologists by Telfer, Colver, and Bowers (1999) recommend the use of curettage and cautery / electrodessication for selected low-risk BCC lesions, but not for recurrent or morphoeic BCC tumours, or BCC tumours in high-risk facial sites. $CO_2$ laser surgery was mainly recommended for low risk lesions and cryosurgery was reported as useful in the treatment of solitary and multiple BCCs but less useful in the treatment of recurrent BCC.

# EVIDENCE TABLE 4.15

***What destructive therapies are available for the treatment of patients with NMSC or premalignant lesions?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Cox *et al.* 1999) | To provide evidence based guidelines for the management of patients with Bowen's disease on behalf of the British Association of Dermatologists. | Clinical guidelines. | Patients with Bowen's disease (SCC in situ).<br><br>**UK** | Recommendations for clinical practice. | **No treatment**<br>For some patients observation alone may be appropriate i.e. elderly patients with lesions on the lower leg where healing is slow.<br><br>**Cryotherapy**<br>Cryotherapy appears to have a good success rate with local recurrences less than 10% at 12 months but healing may be slow for broad lesions and discomfort may limit treatment of multiple lesions.<br><br>**Curettage with cautery/electrocautery**<br>Recurrence rate following curettage with cautery/electrocautery has range zero to 20%, with a failure rate of up to 73%, based upon primary studies. Healing has been demonstrated to be faster following curettage than following cryotherapy with less early pain, but no firm conclusions can be made due to variability of primary studies. | Literature search methods not described.<br><br>Schema included for assessment of evidence quality and grading of recommendations. | 4 + |
| (Motley *et al.* 2003) | To provide evidence based guidelines on the | Clinical guidelines. | Patients with SCC. | Recommendations for clinical practice. | **Curettage and cautery** can produce excellent cure rates in small, (<1 cm) | 82 references cited. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | treatment of patients with SCC on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons. | | **UK** | | well differentiated, primary, slow growing tumours.<br><br>**Cryosurgery** by experienced practitioners can produce good short term cure rates, although prior biopsy is required to ascertain the histological diagnosis, but should be used with caution and is recommended for specialist centres. | Scale for strength of evidence and grade of recommendations included. | |
| (Telfer *et al.* 1999) | To provide evidence based guidelines on the treatment of patients with BCC on behalf of the British Association of Dermatologists. | Clinical guidelines. | Patients with BCC.<br><br>**UK** | Recommendations for clinical practice. | **Destructive surgery**<br>Curettage and cautery / electrodessication is best used for selected low-risk lesions (small, well defined primary lesions with non-aggressive histology usually in non-critical sites, where 5-year cure rates of up to 97% are possible. Curettage and cautery is generally not recommended for the management of recurrent or morphoeic tumours, and tumours in `high-risk' facial sites such as the nose, naso-labial folds and around the eyes.<br><br>Cryosurgery is widely used to treat solitary and multiple BCCs and is less useful in the treatment of recurrent BCC.<br><br>$CO_2$ laser surgery is mainly recommended for low risk lesions. When combined with curettage, $CO_2$ laser surgery may be useful in treating large or multiple, superficial BCCs. | 91 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |

## Systemic Therapy for patients with skin cancer

### Chemotherapy

### The questions

*What is the role of chemotherapy in the treatment of patients with skin cancer?*

### The nature of the evidence

Five studies were identified as follows:

- Three systematic reviews, two of good quality and one of poor quality. One systematic review included a meta-analysis of 20 RCTs.
- Two clinical guidelines of good quality

Three studies were undertaken in the UK, one in the US and the other in Germany. Generalisability to the UK is reasonable, but limited. All studies are of patients with melanoma.

### Summary of the supporting evidence for the recommendations

**Systematic review evidence suggests that there is no RCT evidence to show any overall survival advantage from dacarbazine (DTIC) as a single chemotherapy agent over best supportive care. This is supported by UK clinical guidelines for the treatment of patients with melanoma, which recommend that multiple chemotherapy regimens are used only in the context of clinical trials.**

**Systematic review evidence suggests that single agent DTIC can produce response rates between 5.3% and 28.6%, and that DTIC is regarded by clinicians as having good tolerance by patients and that DTIC plus interferon alpha can increase disease free survival. Evidence from one meta-analysis suggests that regimens of DTIC plus interferon-alpha, DTIC-containing multi-drug regimens and combination drug**

**therapies have increased tumour response rates compared to DTIC alone, but with no difference in overall survival.**

- The Cochrane Systematic Review by Crosby et al. (2004) concluded that there is no evidence from randomised controlled clinical trials to show superiority of systemic therapy over best supportive care / placebo in the treatment of patients with melanoma, although the authors noted that DTIC, when used alone, has partial responses in 15-28% of patients, complete responses in 3-5% and long term remission in less than 2% of patients.

- The systematic review by Eigentler et al. (2003) concluded that in patients with advanced stage melanoma, no polychemotherapy schedules were found to significantly prolong overall survival compared to dacarbazine and that the use of interferon alpha in adjuvant therapy increased disease free survival.

- The meta-analysis by Huncharek, Caubet, and McGarry (2001) which compared single agent DTIC with any chemotherapy combination in patients with stage IV melanoma, concluded that the combination of DTIC and interferon-alpha appears to be more active than standard single-agent DTIC in metastatic melanoma in terms of tumour response rates. No difference in overall survival was demonstrated.

- Evidence based guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists recommend that patients with melanoma of disease stage IIB and over should be referred to a Cancer Centre service for consideration of trials of adjuvant therapies.

- Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) state that Dacarbazine (DTIC) is the standard single agent of choice in the treatment of patients with stage IV melanoma. Multiple regimens including those with tamoxifen and interferon alpha do not improve survival compared to single agent DTIC and are not recommended outside of clinical trials.

# EVIDENCE TABLE 4.16

## *What is the role of chemotherapy in the treatment of patients with skin cancer?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Crosby *et al.* 2004) | To review the benefits from the use of systemic therapies in metastatic cutaneous melanoma compared to best supportive care/placebo, and to establish whether a 'gold standard' therapy exists which is superior to other treatments. | Systematic review.<br><br>Identification and findings of RCTs that meet the inclusion criteria as follows:<br><br>RCTs of adults with histologically proven metastatic cutaneous melanoma in which systemic anti-cancer therapy was compared with placebo or supportive care. | Adults with histologically proven metastatic melanoma.<br><br>**Review undertaken in the UK** | Survival (overall, median and progression free survival).<br><br>Quality of life by QOL tool (EORTC, 1994).<br><br>Response rates.<br><br>Treatment morbidity i.e. toxicity, grade 0-4 (EORTC, 1994). | No RCTs were found comparing a systemic therapy with placebo or best supportive care in metastatic cutaneous melanoma.<br><br>Authors note that clinicians may not be willing to randomise patients to 'no therapy' given the observed effectiveness of DTIC therapy.<br><br>Reviewers' conclusions: There is no evidence from randomised controlled clinical trials to show superiority of systemic therapy over best supportive care/placebo in the treatment of malignant cutaneous melanoma. Given that patients with metastatic melanoma frequently receive systemic therapy, it is our pragmatic view that a future systematic review could compare any systemic treatment, or combination of treatments, to single agent dacarbazine.<br><br>Review observes that DTIC, when used alone, has partial responses in 15-28% of patients, complete responses in 3-5% and long term remission in less than 2% of patients. | A substantive amendment to this systematic review was last made on 22 February 2000.<br><br>Search strategy comprehensive and well reported. | 1 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | It is uncertain whether any additional benefit arises from the use of other chemotherapy agents (e.g. platinum agents, vinca alkaloids, nitrosuria and taxanes) used either alone or in combination regimens.<br><br>It is also uncertain whether any additional benefit arises from the use of cytokines, interferon alpha and interleukin-2 when used with cytotoxic agents. | | |
| (Eigentler *et al.* 2003). | To investigate rates of response to various treatment modalities and the outcome for the patients. | Systematic review of 41 randomised studies in disseminated melanoma. | Patients with advanced stage melanoma.<br><br>**Review undertaken in Germany** | Overall survival. | Authors note general study heterogeneity and that many trials had small sample sizes and did not report a power analysis and not all were analysed by intention to treat.<br><br>No polychemotherapy schedules were found to significantly prolong overall survival compared to dacarbazine. Dacarbazine produced response rates between 5.3% and 28.6%.<br><br>The addition of tamoxifen did not increase response rates or overall survival.<br><br>C Parvum or BCG vaccine also proved ineffective.<br><br>The use of interferon alpha in adjuvant therapy is believed to increase disease free survival and dacarbazine plus interferon alpha produced a response rate of between 14% and 53%.<br><br>Authors conclude that patients with disseminated melanoma should be treated with well-tolerated drug regimens, such as single-agent treatments or in combination with | Review analysed seven studies that compared polychemotherapy with single-agent dacarbazine, six that compared different chemotherapeutic schedules with each other, five on the addition of tamoxifen to a reference therapy, and six that included non-specific immunostimulators. In 17 studies, the addition of interferon alpha, interleukin 2, or both, to a reference therapy was investigated, including trials with biochemotherapy.<br><br>Literature search adequately reported.<br><br>Thorough appraisal of study quality apparent - p values calculated for studies where absent.<br><br>Data largely reported by narrative. | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | interferon alpha. | | |
| (Huncharek *et al.* 2001) | To pool data from studies comparing DTIC as a single agent with combination chemotherapy with or without immunotherapy. | Systematic review and meta-analysis of studies that compared single agent DTIC with any chemotherapy combination, chemotherapy and immunotherapy or tamoxifen. | Patients with stage IV melanoma.<br><br>**Review undertaken in the US** | Tumour response rate.<br><br>Time to tumour progression.<br><br>Overall survival. | 20 studies were eligible for conclusion, representing a total of 2706 analysed patients.<br><br>Combination drug therapies were found to be associated with increased response rate compared with single-agent DTIC (OR 1.23, 95% CI1.02-1.48).<br><br>The combination of DTIC plus interferon-alpha produced greater tumour response rate (OR 1.53, 95% CI 1.10-2.13) than that seen with DTIC alone.<br><br>DTIC-containing multi-drug regimens also showed increased tumour response rate (OR1.33, 95% CI 0.99-1.78).<br><br>No difference in overall survival was demonstrated.<br><br>Non-DTIC-containing treatment programmes showed no advantage over DTIC in terms of tumour response rate (OR = 0.77, 95% CI 0.45-1.32).<br><br>Authors conclude that the combination of DTIC and interferon-alpha appears to be more active than standard single-agent DTIC in metastatic melanoma. | Study eligibility criteria, data elements for extraction and plan for analysis defined at outset.<br><br>Methods adequately reported.<br><br>Studies identified covered the time period from January 1970 to January 1999.<br><br>Statistical analysis was by a fixed effects model designed by Peto et al. (1985). | 1 + |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma. | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where | Stage IIB and over patients should be referred to a Cancer Centre service for consideration of trials of adjuvant therapies. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | evidence is insufficient. | | | |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma. | Recommendations for practice. | Dacarbazine (DTIC) is the standard single agent of choice in stage IV melanoma.<br><br>Multiple regimens including those with tamoxifen and interferon alpha do not improve survival compared to single agent DTIC and are not recommended outside of clinical trials. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |

## Immunotherapy

### The question

*What is the role of immunotherapy in the treatment of patients with skin cancer?*

### The nature of the evidence

Seven studies were identified as follows:

- Two systematic reviews of good quality.
- Three RCTs, one of good quality and two of poor quality.
- Two clinical guidelines of good quality

Four studies originate from the UK and two are from the US, with one study undertaken in Belgium. Generalisability to the UK is reasonable, but limited. All studies are of patients with melanoma.

### Summary of the supporting evidence for the recommendations

**Systematic review evidence consistently suggests that the use of systemic interferon alpha in patients with surgically treated high risk melanoma can improve recurrence free survival, although there is no significant evidence for a benefit in terms of overall survival. A small volume of RCT evidence of vaccination treatment of melanoma has demonstrated no overall survival benefit through the use of a vaccine although there is tentative evidence for an improvement in recurrence-free survival.**

**Evidence based guidelines from the UK recommend that systemic interferon alpha should only be used to treat patients with melanoma within the context of clinical trials and that patients should be offered entry to trials of vaccine therapies.**

- The systematic review and meta-analysis of randomised trials comparing interferon alpha with control in the adjuvant setting by Wheatley et al. (2003) found that recurrence-free survival was improved with interferon-alpha but with no significant difference in terms of overall survival. A significant dose response relationship for recurrence-free survival was observed, but not for overall survival.

- The systematic review of randomised controlled trials of interferon alpha in patients with stage I or II melanoma by Lens and Dawes (2002) concluded that of nine trials, only one adequately demonstrated a statistically significant benefit in disease free survival for the patients treated with interferon alpha and that there is no evidence for increased overall survival arising from interferon alpha.

- The systematic review and meta-analysis by Pirard et al. (2004) found that the use of interferon alpha as an adjuvant therapy for patients with surgically treated melanoma stage I-III, both high and low doses significantly decreased the relapse rate although no significant effect was found in terms of overall survival.

- The small, RCT comparing vaccine therapy with placebo undertaken by Bystryn et al. (2001) concluded that immunization with a melanoma vaccine was able to slow the progression of melanoma with reduced time to recurrence when analysed in a Cox proportional hazards model. No significant effect was observed for overall survival.

- Evidence based guidelines produced on behalf of the British Association of Dermatologists by Roberts et al. (2002) state that the role of interferon as an adjuvant therapy in patients with melanoma remains to be established.

- Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) recommend that adjuvant interferon should not be used for patients with AJCC stage II and III melanoma other

than in a trial setting and that patients should be entered into vaccines trials as appropriate.

- The RCT comparing allogeneic melanoma vaccine against observation in patients with surgically treated melanoma undertaken by Sondak et al. (2002) found no significant difference in disease-free survival between randomisation groups, nor between patients with thick (> 3mm) versus thin (≤ 3mm) tumours.

# EVIDENCE TABLE 4.17

## *What is the role of immunotherapy in the treatment of patients with skin cancer?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Wheatley *et al.* 2003) | To systematically review RCTs comparing interferon-alpha with control as adjuvant therapy for high-risk malignant melanoma. | Systematic review and meta-analysis of randomised trials comparing interferon alpha with control in the adjuvant setting. | Patients with high risk melanoma.<br><br>**Review undertaken in the UK** | Pooled estimate of disease free and overall survival. A subgroup analysis by dose of interferon-alpha was performed. | Twelve trials, comprising 14 comparisons of interferon-alpha with control, were identified.<br><br>Recurrence-free survival was improved with interferon-alpha (hazard ratio (HR) for odds of recurrence 0.83, 95% CI 0.77 to 0.90, p = 0.000003).<br><br>There was no significant difference in terms of overall survival (HR 0.93, 0.85 to 1.02, p = 0.1).<br><br>There was some evidence of a dose response relationship with a significant trend for the benefit of interferon-alpha to increase with increasing dose for recurrence-free survival (test for trend: p = 0.02) but not for overall survival (trend: p = 0.8).<br><br>Authors conclude that adjuvant interferon-alpha produces reductions in recurrence of high-risk melanoma, with some evidence of an effect of dose of interferon-alpha, but it is unclear whether this translates into a worthwhile survival benefit or not. | Studies of interferon alpha with other agents were excluded from inclusion.<br><br>Literature search methods not fully reported but other methods adequately described. | 1 + |
| (Lens & Dawes 2002) | To assess the benefit of | Systematic review | Patients with stage I | Effect of interferon | Nine RCTs of interferon alpha therapy | Literature search rigorous | 1 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | interferon alpha therapy in malignant melanoma. | of RCTs comparing doses of interferon alpha or interferon alpha versus observation as single agent adjuvant therapy in melanoma patients. | - III melanoma with no overt lymph node or distant metastases.<br><br>**Review undertaken in the UK** | alpha therapy on overall survival (OS), disease-free survival (DFS), melanoma recurrences, and toxicity. The quality of each trial was systematically evaluated. | in melanoma patients were identified.<br><br>Eight trials comprising 3,178 patients fulfilled the inclusion criteria and were analyzed. For overall survival, only one trial reported a statistically significant benefit for interferon alpha, but further analysis did not confirm it.<br><br>Two trials reported statistically significant benefit in disease free survival for the patients treated with interferon alpha, but further analysis confirmed it in only one trial.<br><br>There was a wide clinical heterogeneity between included trials, making meta-analysis inappropriate.<br><br>Authors conclude that there is no clear benefit of interferon alpha therapy on overall survival in patients with melanoma. | and well described.<br><br>Good evidence of study appraisal. Two reviewers independently appraised papers and reached consensus for disagreements.<br><br>Study quality assessment undertaken and scored, although scale appears to be designed uniquely for this study - scores ranged from 22 to 71, with a mean score of 55.4 (95% confidence interval, 53.8 to 57.0). | |
| (Pirard *et al.* 2004) | To provide a pooled estimate of the effect of interferon alpha in the treatment of patients with melanoma. | Systematic review and meta-analysis of randomised studies of interferon alpha as an adjuvant therapy compared with control. | Patients with melanoma treated surgically, of disease stage I-III.<br><br>**Review undertaken in Belgium** | Relapse rate.<br><br>Overall survival.<br><br>Effect of dose. | Nine published studies were included, with a total of 2,880 patients.<br><br>No significant heterogeneity was detected.<br><br>Interferon -alpha significantly decreased the relapse rate (OR 0.74; 95% CI 0.64-0.86).<br><br>Subgroup analyses showed that, for all disease stages, high and low doses decreased the relapse rate (OR 0.71, 95% CI 0.54-0.92, and OR 0.76, 95% CI 0.63-0.91, respectively).<br><br>No significance difference was found for overall survival (OR 0.87, 95% CI 0.74-1.02). | Methods adequately reported.<br><br>Two reviewers independently appraised studies.<br><br>English and French Language studies included.<br><br>ITT analysis performed where data available.<br><br>Peto's fixed effects model used. | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Authors conclude that both high and low doses of interferon-alpha significantly decrease the relapse rate, but there is no evidence that overall survival is improved. | | |
| (Bystryn *et al.* 2001) | To assess whether a vaccine given for up to 5 years could slow the progression of resected melanoma compared with placebo vaccine. | RCT comparing vaccine therapy with placebo. | 38 patients with resected stage III melanoma metastatic to regional nodes.<br><br>**US** | Disease free survival.<br><br>Overall survival. | There was no local or systemic toxicity.<br><br>By Kaplan-Meier analysis, median time to disease progression was longer in patients treated with melanoma vaccine compared with that in patients treated with placebo vaccine (1.6 years, 95% CI 1.0-3.0 years compared with 0.6 years, 95% CI 0.3-1.9 years, p = 0.26).<br><br>With subsequent Cox proportional hazards analysis adjusting for known prognostic factors, this finding became statistically significant (p = 0.03).<br><br>Overall survival was 40% longer in the melanoma vaccine-treated group (median overall survival of 3.8 years versus 2.7 years), but this difference was not statistically significant after adjusting for prognostic factors.<br><br>Authors conclude that immunization with the melanoma vaccine may be able to slow the progression of melanoma. | Trial double blinded.<br><br>Randomisation based upon a 2:1 ratio of vaccine : placebo in order to encourage patients to consent to randomisation.<br><br>The groups were evenly balanced with respect to prognostic factors. Median length of observation was 2.5 years.<br><br>Very small study size. | 1 - |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | The role of interferon as an adjuvant therapy remains to be established. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with | Evidence based guidelines, with recommendations graded according | Patients with melanoma.<br><br>**UK** | Recommendations for practice. | Adjuvant interferon should not be used for AJCC stage II and III melanoma patients other than in a trial setting. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | melanoma. | to the quality of evidence available. | | | Patients should be entered into vaccines trials as appropriate. | Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | |
| (Sondak *et al.* 2002) | To test the efficacy of a melanoma vaccine. | RCT comparing allogeneic melanoma vaccine versus observation, over a two year period. | 600 patients with surgically treated melanoma of intermediate-thickness (1.5 to 4.0 mm or Clark's level IV if thickness unknown), clinically or pathologically (where staging was performed) node-negative melanoma (T3N0M0).<br><br>**US** | Disease free survival. | **Toxicity**<br>Most vaccine patients experienced mild to moderate local toxicity, but 26 (9%) experienced grade 3 toxicity.<br><br>**Disease free survival**<br>After a median follow-up of 5.6 years, there were 107 events (tumour recurrences or deaths) among the 300 eligible patients randomised to vaccine compared with 114 among the 300 eligible patients randomised to observation (hazard ratio, 0.92 95% CI 0.70 -1.19). The level of significance of the treatment effect, adjusting for other prognostic factors, was assessed as $P_2$ = 0.51 (Cox model).<br><br>There was no difference in vaccine efficacy between patients with tumours ≤ 3 mm and those with tumours > 3 mm.<br><br>**Overall survival**<br>Not analysed as predetermined level of maturity not reached.<br><br>Authors conclude that there is no evidence of improved disease-free survival among patients randomised to receive vaccine, although the power to detect a small but clinically significant difference was low. | Thirteen eligible patients refused assigned treatment: seven on the observation arm and six on the vaccine arm.<br><br>Surgical node staging was performed in 24% of patients recruited i.e. patients with pathologically as opposed to clinically disease negative regional nodes.<br><br>Randomisation arms were stratified for known prognostic factors including Breslow thickness and method of lymph node staging (clinical or surgical), but not for ulceration.<br><br>Both groups received equal physician contact / follow-up.<br><br>Protocol set out for management / cessation of vaccine due to toxicity.<br><br>Power calculation performed to provide 87% power to detect a 50% increase in disease free survival.<br><br>No evidence of blinding. | 1 + |

## Radiotherapy in patients with skin cancer

### The questions

*What is the role of radiotherapy in the treatment of patients with skin cancer?*

### The nature of the evidence

Twelve studies were identified as follows:

- One systematic review of good quality
- Five observational studies, three of good quality and two of fair quality
- Three clinical guidelines of good quality
- Three expert reviews of fair quality

Five studies are from the UK, three studies are from the US, two studies are from Canada, one study is from France and the remaining study is jointly from Australia and New Zealand. Applicability to the UK is reasonable, but limited.

Four studies are of patients with melanoma and six are of patients with NMSC. Two studies are of patients with cutaneous lymphoma.

### Summary of the supporting evidence for the recommendations

### Non melanoma skin cancer

**Systematic review evidence suggests that radiotherapy is an effective treatment for patients with BCC with local recurrence rates that are favourable to cryotherapy, but less favourable than those seen following surgery. Observational study evidence suggests that high rates of local and regional control can be achieved by radiotherapy for patients with NMSC, but with higher local recurrence rates for SCC. Observational study evidence also suggests that in patients with BCC of the head, face and neck, treated with superficial radiotherapy, the total local recurrence rate is approximately 6%. The same level of evidence suggests that radiotherapy can be effective for controlling nasal SCC. The studies**

**identified therefore suggest that radiotherapy is a useful treatment option for patients with NMSC for whom surgery is inappropriate.**

**Clinical guidelines from the UK for the treatment of patients with BCC state that radiotherapy is an extremely useful form of treatment for BCC and is best performed by clinical oncologists with a specialist interest in skin cancer.**

**Cutaneous lymphoma**

**Evidence from one observational study suggests that for patients with mycosis fungoides total skin electron beam therapy (TSEB) without adjuvant therapy can achieve a response rate of 94.7% with overall survival at 5, 10, and 15 years at 90%, 65% and 42%, respectively. The authors of this study concluded that TSEB is highly effective in early-stage mycosis fungoides. Evidence from one expert review adds that megavoltage radiotherapy can also be used selectively for palliative treatment of extracutaneous disease.**

**Melanoma and lentigo maligna**

**Surgery is the definitive treatment for melanoma. Observational study evidence suggests that where radiotherapy is used to treat patients with melanoma metastatic to the regional node basin, the late toxicity effects are acceptable.**

**Expert review evidence supports the role of low dose radiotherapy with minimal penetration in the treatment of lentigo maligna with control rates of 95% - 100%. The same level of evidence suggests that radiotherapy can reduce the rate of local-regional recurrence of melanoma where, given as an adjunct to surgery following excision of aggressive or recurrent cutaneous melanoma tumours, or as an adjunct to regional lymph node dissection. Radiotherapy has a palliative role in treating patients with melanoma that is metastatic to the brain and visceral organs and also for metastatic spinal cord compression.**

- The expert review by Ballo and Ang (2003) reports that although surgery is the primary treatment for patients with localized melanoma, radiotherapy may be considered as a primary treatment alternative for elderly patients with large facial lentigo maligna melanoma. Radiotherapy may also be considered as an adjuvant to regional lymph node dissection in controlling regional metastatic disease. The optimal dose in many instances remains controversial.

- The systematic review of RCTs of treatments for patients with BCC undertaken by Bath-Hextall, Bong, and Williams (2004) found that significantly more recurrences arose in patients treated with radiotherapy compared with patients treated with surgery. Significantly more recurrences occurred in patients treated by cryotherapy compared to radiotherapy. The authors concluded that surgery and radiotherapy are the most effective treatments for BCC.

- The case series study by Burmeister et al. (2002) found that amongst patients with metastatic melanoma in the regional node basin who were treated with post operative radiotherapy, 7.1% of patients with axillary disease and 18.2 of patients with inguinal/iliac disease developed lymphoedema. The authors concluded that the results of late toxicity experienced in the study were acceptable and should warrant a prospective, randomised trial.

- The expert review by Cooper (2002) reported that approximately one fourth of palliatively irradiated malignant melanoma tumours respond completely and that one third respond substantially. Radiotherapy can achieve control rates of 95% - 100% of Lentigo maligna tumours. Local-regional recurrence of melanoma may be reduced by elective radiotherapy following resection of large, aggressive tumours or lymphatic metastases.

- The expert review by Hoppe (2003) stated that radiotherapy is the most effective single agent for the treatment of mycosis fungoides, with total skin electron beam therapy (TSEB) as an important form of

management, especially for patients who have widespread disease. Megavoltage radiotherapy may also be used selectively for palliative treatment of extracutaneous disease.

- The retrospective case series study of patients treated with radical radiotherapy for SCC or BCC undertaken by Kwan, Wilson, and Moravan (2004) found the four-year locoregional control rates to be 86% and 58% for BCC and SCC respectively and concluded that BCCs can be well controlled with radiotherapy even when locally advanced whereas SCCs have a much poorer outcome and can recur quickly after radiotherapy.

- Clinical guidelines produced on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons by Motley et al. (2003) state that radiotherapy is an effective treatment for SCC and may be used alone for tumour sites including the lip, nasal vestibule and ear, and that radiotherapy is useful for certain advanced tumours where surgical morbidity may be high.

- The large case series study by Orton (1978) of patients with BCC of the head, face and neck, treated with superficial radiotherapy, found the total local recurrence rate to be 6.1%. The majority of local recurrences occurred in the first three years after treatment but also occurred at low incidence up to ten years after treatment. The author concluded that superficial radiotherapy is efficient for treating elderly patients with BCC, but with higher recurrence rates for difficult facial anatomical sites and poorer cosmetic outcome than that arising from surgery.

- Evidence based guidelines produced by the Scottish Intercollegiate Guidelines Network (2003) do not recommend routine use of adjuvant radiotherapy in patients with melanoma who have had therapeutic lymph node dissections, whereas single dose radiotherapy of at least 8 Gy is an effective treatment for patients with melanoma metastatic to bone.

- Clinical guidelines for the treatment of patients with BCC produced on behalf of the British Association of Dermatologists by Telfer, Colver, and Bowers (1999) state that radiotherapy is an extremely useful form of treatment for BCC, but that radiotherapy faces the same problem of accurately identifying tumour margins as standard excisional surgery. Radiotherapy is best performed by clinical oncologists with a specialist interest in skin cancer.

- The retrospective case series study by Tsao et al. (2002) found that in patients with SCC of nasal skin who were treated by radiotherapy, the local relapse-free rate was 90% and 85% at 2 and 5 years, respectively and the cause-specific survival (median age 74.5 years) was 96% at both 2 and 5 years.

- The retrospective case series study of patients with mycosis fungoides undertaken by Ysebaert et al. (2004) found that at three months after TSEB, the overall response rate was 94.7%. A complete response was achieved in 87.5% of patients with disease affecting < 10% of skin and 84.8% in patients with disease affecting >10% of skin. 5-year disease free survival was 50%. Overall survival at 5/10/15 years was 90%/65%/42%, respectively. The authors concluded that TSEB is highly effective in early-stage mycosis fungoides without adjuvant therapy.

# EVIDENCE TABLE 4.18

***What is the role of radiotherapy in the treatment of patients with skin cancer?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Ballo & Ang 2003) | To review the role of radiotherapy in the treatment of melanoma. | Literature review. | Patients with melanoma.<br><br>**US** | Findings of primary studies. | Surgery remains the primary treatment for patients with localized melanoma.<br><br>The impact of elective/adjuvant radiotherapy on the incidence of distant metastasis and overall survival has yet to be determined.<br><br>There is a role for radiotherapy as a primary treatment alternative for elderly patients with large facial lentigo maligna melanoma based upon studies reporting high rates of tumour regression.<br><br>Local radiotherapy may be applied to the tumour site after excision where high risk features were present, i.e. head and neck desmoplastic primaries, thick or ulcerated tumours, positive surgical margins, locally recurrent tumours.<br><br>Radiotherapy is also useful for dermal, subcutaneous, brain, visceral and bone metastatic disease as well as for spinal cord compression.<br><br>After regional lymph node dissection of | No description of methods, but authors have recommended therapy with the extent and quality of evidence in mind. | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | the neck, radiotherapy can achieve better regional control, based upon one prospective trial.<br><br>Regional radiotherapy to the groin following inguinal lymph node dissection is less frequently performed due to the risk of lower limb lymphoedema.<br><br>The optimal radiation fractionation schedule remains controversial. | | |
| (Bath-Hextall *et al.* 2004) | To assess the effects of treatments for BCC. | Systematic review of RCTs. | Adult patients with histologically proven, primary BCC.<br><br>**UK** | Local recurrence of BCC at 3-5 years, assessed clinically. | 25 studies were identified, covering seven therapeutic categories.<br><br>Only one study of surgical excision versus radiotherapy contained primary outcome data, which showed significantly more persistent tumours and recurrences in the radiotherapy group compared with surgery (odds ratio 0.09, 95% confidence interval 0.01 to 0.67).<br><br>In a comparison of radiotherapy with cryotherapy, significantly more recurrences occurred at one year in the cryotherapy group.<br><br>Surgery and radiotherapy seem to be the most effective treatments; surgery showed the lowest failure rates. Other treatments might have some use but need to be compared with surgery. | Literature search, inclusion criteria, appraisal criteria and meta-analysis method (fixed effects model) very well described. | 1 ++ |
| (Burmeister *et al.* 2002) | To report on the side effects noted in a case series of 130 patients who received adjuvant radiotherapy following resection of malignant melanoma involving regional lymph nodes. | Case series (pilot study). The patients were given adjuvant radiotherapy to a recommended dose of 48 Gy in 20 fractions over 4 weeks. | Patients with melanoma metastasis in a regional node basin.<br><br>Median age 55 years (range 20-89 years).<br><br>**Australia/New** | Late toxicity of the treatment. | Authors note that in the US and Australia, radiotherapy is commonly offered to patients surgically treated for high risk melanoma, based upon retrospective evidence.<br><br>Median dose recorded was 48 Gy in 20 fractions over 4 weeks (range 45-50 Gy). | | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | **Zealand** | | 7.1% of patients with axillary disease and 18.2 of patients with inguinal / iliac disease developed lymphoedema. The mean time to development of lymphoedema was 14.7 months.<br><br>Risk increase of grade 3 lymphoedema estimated at 48% at 4 years for inguinal / iliac sites and 10% at 20 months for axillary supraclavicular sites.<br><br>The results of late toxicity experienced in the study were acceptable. Author concludes that the regimen of 48 Gy in 20 fractions over 4 weeks could form the basis for the treatment arm of a randomised trial. | | |
| (Cooper 2002) | To discuss the role of radiotherapy in treating patients with melanoma. | Expert review (31 references). | Patients with melanoma who are treated palliatively.<br><br>**US** | Outcomes on efficacy of radiotherapy, based upon primary studies. | Approximately one fourth of palliatively irradiated malignant melanomas respond completely and another one third respond substantially.<br><br>Responses of metastatic melanoma tumours in brain and bone are reported as similar to other radiosensitive neoplasms.<br><br>Radiotherapy can achieve control rates of 95% - 100% of Lentigo maligna tumours.<br><br>Radiotherapy has been found to have a useful role in treating sites of surgical excision of intracerebral metastatic melanoma, with improved outcome in both intracerebral recurrence and survival.<br><br>Elective irradiation of anatomic sites considered likely to harbour microscopic-size tumour (i.e. following resection of large, aggressive tumours or lymphatic metastases) decreases the | | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | risk of local-regional recurrence.<br><br>The inability of available systemic therapies, however, to prevent the appearance of distant metastases limits the current impact of such treatment. | | |
| (Hoppe 2003) | To review the role of radiotherapy in the treatment of mycosis fungoides. | Expert review (49 references). | Patients with mycosis fungoides.<br><br>**US** | Outcomes on efficacy and development of techniques in radiotherapy, based upon primary studies. | Radiotherapy is the most effective single agent for the treatment of mycosis fungoides.<br><br>There are well-defined dose-response relationships for achieving a complete response as well as the durability of this response. Complete responses generally require doses of 7 Gy or higher and for total skin electron beam therapy (TSEB), 94% response rates can be achieved for doses of 30 Gy or higher.<br><br>Techniques of electron beam therapy have been developed that permit treatment of the entire skin.<br><br>TSEB is an important form of management, especially for patients who have thick generalized plaque or tumourous disease, although the palliative role is generally more accepted than the disputed curative role. Following TSEB, 25% of patients with extensive plaques can be disease free at 5 years.<br><br>Megavoltage radiotherapy may also be used selectively for palliative treatment of extracutaneous disease. | | 4 |
| (Kwan *et al.* 2004) | To report on outcomes for patients with BCC or SCC who were treated by radiotherapy at a single centre in Canada. | Retrospective case series. | 182 patients treated with radical radiotherapy for SCC or BCC (with T2 or node positive disease) from 1994- | Overall survival.<br><br>Disease specific survival.<br><br>Loco regional | Median patient age was 78 years range 31-103) since most were patients with advanced disease, who were not candidates for surgery.<br><br>Four-year locoregional controls for BCC | Kaplan Meier curves constructed and log rank statistics used for univariate analysis.<br><br>Cox regression performed for | 3 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | 1998.<br><br>61 patients had BCC and 121 patients had SCC.<br><br>**Canada** | failure rate (recurrence). | and SCC were 86% and 58%, respectively.<br><br>The median time to recurrence BCC and SCC were 40.5 months and 5.0 months, respectively.<br><br>No deaths resulted from BCC, but 65% (30/46) of all patients with locoregional recurrent SCC died from the disease.<br><br>Uncontrolled locoregional disease was the cause of death in 81% (30/37) of all patients who died of SCC.<br><br>Authors conclude that BCCs can be well controlled with radiotherapy even when locally advanced. SCCs have a much poorer outcome and can recur quickly after radiotherapy. Locoregional failure remains the predominant cause of death in recurrent SCC. | factors with $p < 0.2$ from univariate analysis. | |
| (Motley *et al.* 2003) | To provide evidence based guidelines on the treatment of patients with SCC on behalf of the British Association of Dermatologists and the British Association of Plastic Surgeons. | Clinical guidelines. | Patients with SCC.<br><br>**UK** | Recommendations for clinical practice. | Radiotherapy is an effective treatment for SCC and may be used alone for tumour sites including the lip, nasal vestibule and ear. Radiotherapy is useful for certain advanced tumours where surgical morbidity may be high. | 82 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Orton 1978) | To report on a large case series of patients with BCC treated by a specific method of superficial radiotherapy at a single centre. | Retrospective case series. | 1790 patients with BCC treated with superficial radiotherapy at a single hospital.<br><br>The majority of patients were aged between 40 and 80.<br><br>**UK** | Total (first) recurrence rate.<br><br>Second recurrence rate. | 1790 of 1879 patients were treated primarily with radiotherapy, the remainder receiving surgery as primary treatment, or refusing treatment.<br><br>The total local recurrence rate in the 1790 cases was 6.1% (110) of which 2.6% represented lesions that had never completely regressed after treatment.<br><br>The majority of local recurrences occurred in the first three years after | Study undertaken at the Christie hospital, where it is reported that the majority (95% on the data presented) of patients with BCC are treated with radiotherapy as the primary treatment.<br><br>Data presented for the years 1966 – 1967 on the grounds of providing lengthy follow-up information. Data are thus reported for a particular two | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | treatment but occurred at low incidence up to ten years after treatment.<br><br>Of the 350 peri-orbital lesions treated in this series, 10% of patients developed epiphora, often permanently. Almost 10% of patients developed minor skin necrosis.<br><br>110 / 1790 cases treated with radiotherapy recurred (i.e. 6.1%), of which 21 were patients who refused subsequent surgery or who were not considered candidates for surgery on the grounds of their age.<br><br>In the 89 patients who underwent subsequent surgery for recurrent BCC, the second recurrence rate was 9.0%.<br><br>Author concludes that the superficial radiotherapy method is efficient for elderly patients with BCC, but with higher recurrence rates for difficult facial anatomical sites and poorer cosmetic outcome than that arising from surgery. | year period, in hindsight.<br><br>Standard treatment was 22.5 Gy at 100 kV, reduced to 18 - 20 Gy at 45 kV for patients with thin skin, in a single fraction.<br><br>Reporting of second recurrence rate is based upon 89 patients who received subsequent surgery for locally recurrent BCC following radiotherapy as the initial treatment. No further outcomes are reported for the 21 patients who did not receive subsequent surgery for recurrent BCC. | |
| (Scottish Intercollegiate Guidelines Network 2003) | To provide advice to health professionals involved at all stages of care of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Recommendations for practice. | The routine use of adjuvant radiotherapy is not recommended for patients who have had therapeutic lymph node dissections.<br><br>Single dose radiotherapy of at least 8 Gy is an effective treatment for bone metastases. | Guideline development was based upon a multidisciplinary Guideline Development Group of experts.<br><br>Development of recommendations included systematic literature review, consultation and peer review.<br><br>Recommendations are graded and grading scheme is reported. | 4 ++ |
| (Telfer *et al.* 1999) | To provide evidence based guidelines on the treatment of patients with BCC on behalf of the | Clinical guidelines. | Patients with BCC.<br><br>**UK** | Recommendations for clinical practice. | Radiotherapy is an extremely useful form of treatment, but faces the same problem of accurately identifying tumour margins as standard excisional surgery. | 91 references cited.<br><br>Scale for strength of evidence and grade of | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | British Association of Dermatologists. | | | | Radiotherapy is best performed by clinical oncologists with a specialist interest in skin cancer.<br><br>Collaboration between dermatologists, plastic surgeons and clinical oncologists in the management of patients with high-risk BCC is a common and valuable feature of dermatological care in the U.K. | recommendations included. | |
| (Tsao *et al*. 2002) | To evaluate the outcome of radiotherapy (RT) for SCC of the nasal skin, primarily with regard to local control and secondarily with regard to survival. | Retrospective case series by review of medical notes. | 94 patients with SCC of nasal skin.<br><br>Median age 74.5 years (range 42-93 years).<br><br>Patients were treated by radiotherapy to the primary lesion without intentional coverage of the regional lymph nodes.<br><br>**Canada** | Local control rates.<br><br>Actuarial and cause specific survival. | The local relapse-free rate was 90% and 85% at 2 and 5 years, respectively.<br><br>The actuarial 2 and 5-year overall survival rate was 75% and 51%, respectively.<br><br>The cause-specific survival was 96% at both 2 and 5 years.<br><br>No Radiotherapy Oncology Group Grade 4 toxicities occurred.<br><br>Univariate analysis could not identify any patient, tumour, or treatment factors that were statistically significant prognosticators.<br><br>Authors conclude that radiotherapy for SCC of nasal skin achieves excellent outcome, is well tolerated, and should continue to be recommended in the management of this disease. | Six patients were lost to follow-up after radiotherapy leaving 94 in the analysis.<br><br>67% of patients received radiotherapy alone and 33% of patients received surgery with post operative radiotherapy.<br><br>Median follow-up was 2.9 years (range 0.2-10.4 years).<br><br>Lesions <=2 cm were treated to 35 Gy in 5 fractions. For tumours 2-5 cm, 45 Gy in 10 fractions was commonly used. Lesions >5 cm or those associated with bone or cartilage invasion were typically treated to 50 Gy in 20 fractions.<br><br>Using the UICC staging system, the T stage at first presentation was as follows: T1, 60 patients; T2, 11 patients; T3, 0 patients, T4, 7 patients; TX, 16 patients. Only 1 patient had regional lymph | 3 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | node disease at presentation. | |
| (Ysebaert *et al.* 2004) | To report on the experience of a single institution in the treatment of T1 and T2 mycosis fungoides (MF) with total skin electron beam therapy (TSEB). | Retrospective case series. | 141 patients with histologically proven mycosis fungoides were referred to the radiotherapy department for treatment by TSEB.<br><br>Mean total dose was 30 Gy, 2 Gy/day, 4 days/week, for 4 weeks.<br><br>Median age was 61 years (range, 19-84).<br><br>**France** | Response measured at three months after TSEB.<br><br>Relapse-free rate, overall survival rate, and management of recurrence.<br><br>Outcomes reported by proportion of involved skin:<br><br>T1: < 10%<br>T2: >10%. | Three months after completion of TSEB, the overall response rate was 94.7%. A complete response was achieved in 87.5% of T1 and 84.8% of T2 patients.<br><br>Thirty-one patients (54.4%) experienced a skin failure (8 with T1 and 23 with T2 disease) within 1 year. 18/ 31 patients received further TSEB as salvage.<br><br>After a second course of TSEB (4 T1 and 10 T2 patients), the 5-year freedom from relapse rate was 70% vs. 39% in patients having received other treatments.<br><br>For the whole group, 5-year disease free survival was 50%. The 5/10/15-year overall survival were 90%/65%/42%, respectively.<br><br>In univariate analysis, T1 ($p = 0.03$), complete response after first TSEB ($p = 0.04$), and age younger than 60 ($p < 0.001$) were significant prognostic factors for overall survival.<br><br>In multivariate analysis, age younger than 60 years was statistically associated with improved overall survival ($p = 0.001$) whereas T stage and complete response were not significant ($p = 0.059$ and $p = 0.063$, respectively).<br><br>During the mean 86-month period of follow-up from relapse, a second recurrence was observed in 29% of patients. | Prior to TSEB 43.8% of patients had received steroids, chemotherapy, retinoids or interferon, but no patients had received prior radiotherapy.<br><br>Some patients also received adjuvant or salvage therapy.<br><br>Kaplan Meier methods used for survival analysis.<br><br>Median follow-up was 114 months (range, 14-300). | 3 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Authors conclude that TSEB is highly effective in early-stage MF without adjuvant therapy. Management of relapses with local radiotherapy or second TSEB is feasible, time-saving, and cost effective. | | |

## In-transit metastases in patients with melanoma

### The question

*What is the optimal management of patients with in-transit metastases arising from melanoma?*

### The nature of the evidence

**Three studies were identified as follows:**

- One systematic review of poor quality
- One case series of fair quality
- One expert review of good quality

The two reviews were undertaken in the UK and the case series originates from Germany. Applicability to the UK is reasonable. All studies are of patients with disseminated metastatic melanoma.

### Summary of the supporting evidence for the recommendations

**Evidence from one expert review is supportive of complete surgical excision of in-transit metastases as the primary treatment. $CO_2$ laser therapy is reported as a useful ablative therapy for numerous, small in-transit metastases and has the advantage of being widely available in hospitals. Isolated limb perfusion (ILP) is a complex surgical procedure with considerable risk of side effects.**

**Evidence from one systematic review of RCTs suggests that ILP with melphalan can be used as a treatment for local disease control where other forms of locoregional therapy are not suitable.**

**Evidence from one observational suggests that treating cutaneous and soft tissue melanoma metastases with intralesional injection of interleukin-2 is safe, and is an effective alternative to conventional therapies.**

- The expert review by Hayes et al. (2004) reported that the aim of treating in-transit metastatic melanoma is palliative, with complete (rather than wide) surgical excision as the first line of treatment. $CO_2$ laser therapy is useful for numerous, small tumours and ILP should be reserved for advanced, in-transit disease when simpler methods of control have been exhausted. Response rates of ILP in the management of in-transit metastatic melanoma were reported with range 48%-91%. Side effects from ILP may be considerable.

- The systematic review by Lens and Dawes (2003) concluded that that prophylactic ILP with melphalan should not be recommended as a routine adjunct to standard surgery in high risk primary limb melanoma and should be used only as a treatment for local disease control if other forms of locoregional therapy are not available.

- The prospective case series study by Radny et al. (2003) examined the use of intralesional injection of interleukin-2 in 24 patients with AJCC stage III or IV melanoma. Complete response of the treated metastases was achieved in 15 patients (62.5%), the longest remission lasting 38 months to the date of reporting. In five patients, partial response was achieved (21%). The authors concluded that the treatment is a safe and effective alternative to conventional therapies.

# EVIDENCE TABLE 4.19

***What is the optimal management of patients with in-transit metastases arising from melanoma?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Lens & Dawes 2003) | To systematically review high quality evidence for the role of isolated limb perfusion with Melphalan in the treatment of patients with melanoma. | Systematic review of 4 RCTs comparing surgery plus prophylactic isolated limb perfusion versus surgery alone. | Patients with histologically confirmed melanoma of the limbs with Anderson stage I to III.<br><br>A total of 522 patients were randomised to surgery plus hyperthermic ILP with melphalan and 516 to surgery alone.<br><br>**Review undertaken in the UK.** | For prophylactic perfusion: overall survival, relapse rate, toxic effects.<br><br>For therapeutic perfusion: complete remission rate, partial remission rate, overall survival.<br><br>Relative risk reduction and 95% CI calculated for each outcome measure. | Four trials of ILP in the prophylactic setting were included.<br><br>Median follow-up had range 39 months to 6.4 years.<br><br>**Survival**<br>Whilst 2 trials reported a statistically significant overall survival advantage, no trial had sufficient power to demonstrate a statistically significant advantage in overall survival.<br><br>**Relapse**<br>31.0% of patients had relapse of disease in the treatment groups compared with 41.3% in the control groups. Only one trial reported a statistically significant decrease in disease progression in the ILP arm.<br><br>One trial reported a significant decrease in the occurrence of in-transit metastases in the ILP group, with NNT=31, 95% CI 17-281).<br><br>**Toxicity**<br>The risk of amputation due to toxicity based on one study was 0.005%. | No studies were identified for the therapeutic role of ILP i.e. in patients with overt metastases.<br><br>Search strategy (with no language restriction) and all other methods well reported.<br><br>Contact sought with authors to clarify primary data.<br><br>Appraisal undertaken independently by two reviewers.<br><br>Authors refer to further studies aside those which met the inclusion criteria. | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Authors conclude that prophylactic ILP should not be recommended as a routine adjunct to standard surgery in high risk primary limb melanoma and should be used only as a treatment for local disease control if other forms of locoregional therapy are not available. | | |
| (Hayes *et al.* 2004) | To review evidence on treatments for in-transit metastasis arising from melanoma. | Expert review (90 references). | Patients with in-transit melanoma.<br><br>**Review undertaken in the UK** | Recommendations for practice based upon authors' experience and review of published studies. | In-transit metastases are a marker of aggressive primary disease and may increase in number over time and accelerated occurrence of in-transit disease is often followed by distant metastases.<br><br>Randomised studies have shown no association between excision margin of the primary tumour and the likelihood of in-transit metastases.<br><br>There is no requirement for in-transit tumours to be excised with a wide surgical margin and the surgical aim should be macroscopic complete excision with primary wound closure.<br><br>$CO_2$ laser therapy is of value in the treatment of multiple, small volume in-transit metastases that are too numerous to be treated by surgical excision. Studies have reported treating patients with a median of 30 lesions per patient.<br><br>ILP can introduce cytotoxic agents to a single limb at doses of up to ten times that which can be administered systemically. Uncontrolled studies report response rates of 48%-91%. Side effects to the limb range from mild erythema to deep tissue damage and compartment syndrome. Systemic | | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | leakage of the cytotoxic agent can cause hypotension and myelosupression. Melphalan is the most commonly used agent, the action of which may be potentiated by the inclusion of TNF-alpha.<br><br>Authors conclude that the aim of treating in-transit metastatic melanoma is palliative, with complete (rather than wide) surgical excision as the first line of treatment. CO2 laser therapy is useful for numerous, small tumours and ILP should be reserved for advanced, in-transit disease when simpler methods of control have been exhausted. | | |
| (Radny *et al.* 2003) | To validate the use of intralesional injection of interleukin-2 in patients with skin and soft-tissue melanoma metastases.<br><br>Interleukin-2 injections were administered intralesionally into the total number of cutaneous and soft-tissue metastases accessible from the skin, 2-3 times weekly, over 1-57 weeks. | Prospective case series. | 24 patients with AJCC stage III or IV melanoma and single or multiple skin and soft-tissue metastases.<br><br>**Germany** | Complete response rate of lesions.<br><br>Partial response rate of lesions.<br><br>Survival. | **Patients:**<br>Complete response of the treated metastases was achieved in 15 patients (62.5%), the longest remission lasting 38 months to the date of reporting. In five patients, partial response was achieved (21%) and in another three patients, progressive disease was observed (one patient was not assessable).<br><br>**Lesions:**<br>A total of 245 metastases were treated with complete response in 209 (85%), and partial response in 21 (6%).<br><br>**Survival:**<br>For patients with stage III disease the 2 year survival rate was 100% and the 5 year survival rate was 63%. For patients with stage IV disease the 1 year survival rate was 63% and the 2 year survival rate was 33%.<br><br>**Side effects:** | The clinical response was monitored by sonography and confirmed by histopathology; response evaluation was confined to the intralesionally treated tumours. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | The therapy was generally well tolerated. All patients experienced local erythema and swelling. The majority also reported pain due to injections, fever and flu-like symptoms with night sweats. The observed adverse events were mainly of WHO adverse event grade 1-2 severity.<br><br>Authors conclude that the treatment of skin and soft-tissue melanoma metastases with intralesional injection of interleukin-2 may be a safe and effective alternative to conventional therapies. The optimal dosage and duration of this therapy still remain to be defined in larger prospective multi-centre trials. | | |

# Chapter 5 – Follow-up of Patients with Skin Cancer

## Non melanoma skin cancer

### The questions

*In patients with successfully treated BCC, how effective is follow-up in secondary care in detecting recurrence?*

*In patients with successfully treated BCC, how effective is follow-up in secondary care in detecting metachronous tumours?*

*In patients with successfully treated primary SCC how effective is follow-up in secondary care in improving survival?*

*In patients with successfully treated primary SCC, how effective is follow-up in secondary care in detecting recurrence?*

### The nature of the evidence

Nine studies were identified which address the follow-up of patients with NMSC, as follows:

- One systematic review, of good quality
- One cohort study of poor quality
- Seven observational studies of fair quality

Three studies originate from the UK, four studies are from the US and two studies are from Australia. Generalisability to the UK is therefore limited. Eight studies are of patients with NMSC, whereas one study is of the follow-up practice of dermatologists.

### Summary of the supporting evidence for the recommendations

### Non melanoma skin cancer

**Three observational studies were identified which address follow-up of patients with tumours grouped as NMSC. The findings of these studies are that patients diagnosed with NMSC are at greater risk of developing metachronous skin cancer, with reported rates of risk ranging from 35% to 67.8%. Metachronous tumours are usually cytologically the same as the previous cancer but also include melanoma. The relative risk of developing melanoma in patients with a history of NMSC is estimated as 17 times that of an individual with no history of NMSC by Marghoob et al. (1995). There is evidence to support careful follow-up of patients with multiple NMSC.**

- The case series study by Czarnecki et al. (2002) found that further, metachronous skin cancer developed in 67.8% of patients with a history of NMSC and subsequent tumours included SCC in 36% of patients and melanoma in 4.7%. Risk factors for new skin cancer formation were male gender and multiple skin cancers and the authors recommended particularly careful follow-up in patients with multiple NMSC.

- The case series study by Karagas et al. (1992) estimated the risk amongst patients with a history of NMSC of developing one or more metachronous skin cancers as 35% at 3 years and 50% at 5 years follow-up. The type of metachronous tumour was usually cytologically the same as the previous cancer.

- The historical cohort study by Marghoob et al. (1995) estimated the relative risk of developing melanoma in patients with history of BCC or SCC as 17, suggesting that regular and life-long surveillance with total cutaneous examination is an inexpensive and effective method for detecting melanoma.

**BCC**

**Four observational studies and one systematic review were selected on the follow-up of patients with BCC alone. There is evidence that dermatologists vary in their extent of follow-up of patients with BCC due**

**to pressure on clinic time. Observational study evidence from the US suggests that patients with a history of BCC are at increased risk of developing metachronous BCC compared with the risk of BCC in the general US population. The majority of local BCC recurrences are within the first five years following treatment, but local recurrence can occur beyond 5 years, and is more likely where excision of the primary tumour is incomplete. Studies are inconsistent in recommending follow-up periods for patients with BCC, which range from zero assuming complete excision, to lifetime follow-up.**

- The cross sectional survey by Bower, Lear, and de Berker (2001) found that UK dermatologists varied in their self reported follow-up of 'well-defined' BCC from inside a central 'T' area on the face. This study also found that dermatologists do not follow-up all BCC patients since clinics are too full and 92% reported follow-up for all patients with Gorlin's Syndrome.

- The retrospective case series study by Marghoob et al. (1993) found that patients with a history of BCC were at significantly greater risk of developing metachronous BCC, compared with the risk of BCC in the general white skinned US population. The authors recommended life-long follow-up for patients with a history of BCC.

- The case series study by Park, Strick, and Watson (1994) found the overall local recurrence rate of BCC to be 5.1% with 39% of lesions recurring if the tumour was incompletely excised compared with 1% if it was excised completely. The study concluded that complete excision is key to surgical control and there is no need to follow-up patients routinely if the BCC has been completely excised.

- The systematic review by Rowe et al. (1989) found that whilst the majority of BCC local recurrences occur within 3 years following treatment, 18% appear between the fifth and tenth year, irrespective of treatment modality. The authors concluded that lifetime follow-up is necessary after treatment of BCC.

- An audit by Thomas, McKiernan, and Rao (1996) found no definite correlation between histological type of BCC and local recurrence of BCC. Local recurrence was observed to occur from 2 years, thereafter the frequency of tumours increased. The authors concluded that all patients with excised BCC should be followed up for at least 3 years.

**SCC**

**Two studies were identified which consider the follow-up of patients with SCC alone. Systematic review evidence suggests that SCC has capacity to recur locally and also to metastasise, and that local recurrence rate increases with increased duration of follow-up, with a higher recurrence rate for tumours of the ear than the lip. The two studies identified vary in their recommendation for follow-up of patients treated for SCC, ranging from a minimum of two years to lifetime follow-up.**

- The case series study by Nixon, Dorevitch, and Marks (1986) found that in patients diagnosed with SCC, 4 out of 297 tumours metastasised with mean duration between excision and metastasis 10.3 months and18 out of 297 tumours recurred locally with mean duration between excision and recurrence 7.7 months. The rate of metastasis was 2% overall and the authors suggested a follow-up of at least 2 years after treatment.

- The systematic review by Rowe, Carroll, and Day, Jr. (1989) found that the local recurrence rate increased with increased duration of follow-up. Local recurrence rate for SCC of the lip was 7.6% to 10.5% and for SCC of the ear 16.1% to 18.7%. The metastatic rate for SCC of the lip was 7.2% to 13.7%. Some recurrences and metastases were observed more than 5 years after treatment and the authors strongly recommended that patients with SCC should have lifetime follow-up.

# EVIDENCE TABLE 5.1

***In patients with successfully treated BCC, how effective is follow-up in secondary care in detecting recurrence?***

***In patients with successfully treated BCC, how effective is follow-up in secondary care in detecting metachronous tumours?***

***In patients with successfully treated primary SCC how effective is follow-up in secondary care in improving survival?***

***In patients with successfully treated primary SCC, how effective is follow-up in secondary care in detecting recurrence?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bower *et al.* 2001) | To investigate the follow-up intentions of U.K. dermatologists for well-defined facial BCC and to investigate the effect that variations in site and clinical indicators might have on those intentions. | Cross-sectional survey. | 388 dermatology consultants and associate specialists in the UK.<br><br>**UK** | Self-reported BCC follow-up practices. | 27% of respondents reported that they would not review further after excision of a 'well-defined' BCC from inside a central 'T' area on the face; 37% reported that they would review on one occasion; and 36% reported that they review more than once.<br>Strongest agreement was with statement “Clinics are too full to follow all patients”, with 47% selecting highest level of agreement on 7 point scale<br>Gorlin’s syndrome had most significant impact on decision to follow-up (92% indicating 100% follow-up). | 264 respondents (68%) with 246 suitable for analysis.<br><br>Paper goes on to discuss purpose of follow-up – monitor for recurrence; occurrence of new lesions; monitor of outcomes; patient education; check for post-operative morbidity and cosmetic acceptability. | 3 |
| (Czarnecki *et al.* 2002) | To determine the incidence of new skin | Case series. | 481 patients with NMSC (300 were | Metachronous skin cancer formation | Another skin cancer developed in 67.8% and multiple skin cancers 3 or | Comparisons made with general population used data | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | cancer formation in people who have had a NMSC removed. | | followed for at least 10 years).<br><br>**Australia** | (of any type). | more) in 51.8%. Logistical regression analysis found the main risk factors for new skin cancer formation were male sex and if the patient had multiple skin cancers.<br><br>An SCC developed in 36% during the study and a melanoma in 4.7% of men and 2.1% of women. Men who had a NMSC were 8 times more likely than the general population to develop a melanoma while women with NMSC were 4 times more likely. 3 patients died of metastatic SCC and one of metastatic melanoma during the follow-up period. Multivariate analysis showed that multiple skin cancer formation was the main risk factor for SCC or melanoma formation. | from the Cancer registry for the same area.<br><br>Authors suggest that patients with NMSC require careful follow-up due to increased risk of new cancer formation. Those with multiple NMSC merit particularly careful follow-up as all develop another NMSC within 10 years and have significantly increased risk of developing SCC or melanoma. | |
| (Karagas *et al.* 1992) | To assess risk of subsequent basal and squamous cell skin cancer among patients with a prior history of these tumours and to examine these risks in relation to patient characteristics and life-style factors. | Case series follow-up of patients in an RCT of beta carotene as a potential skin cancer preventive agent. | 1805 patients diagnosed with BCC or SCC between 1980-1986, but who were free from skin cancer at study entry.<br><br>Follow-up of 5 years or until 1989.<br><br>**US** | Time from study entry to first metachronous occurrence of BCC/SCC. | Estimated risk of developing one or more new skin cancers was 35% at 3 years and 50% at 5 years. New skin cancers tended to be of the same cell type as the previous skin cancers. For both BCC/SCC, risk was higher among patients who were male, were over the age of 60 years, had more prior skin cancers, had severe actinic skin damage, or who burned easily with sun exposure. | Recall bias likely for lifestyle factors.<br><br>Authors conclude that there is a need for continued follow-up. Those with history of NMSCs and those with more severe sun damage and sun-sensitive skin type require closest scrutiny. | 3 |
| (Marghoob *et al.* 1995) | To determine the risk of developing melanoma in patients with history of BCC or SCC and to determine whether surveillance efforts can be directed toward these patients for detection of early melanoma tumours. | Historical cohort. | 290 patients with history of BCC or SCC followed by annual total cutaneous examination (TCE).<br><br>Control from US population matched for age, sex and length of follow-up | Relative risk of developing metachronous melanoma. | 10 of 290 patients developed an melanoma within an average of 109 months of follow-up (range 3-17 years). 80% occurred on usually clothed sites. Expected number of melanoma tumours in control population was 0.59 (p = 0.006), giving a RR=17. | Authors suggest that regular and life-long surveillance TCE is an inexpensive and effective method for detecting melanoma tumours.<br><br>Insufficient know about controls to assess – from general population of US rather than area local to study patients. | 2- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | Follow-up:<br>Mean 98.5 months (range 12-576 months).<br><br>**US** | | | Study excluded patients with a history of melanoma. | |
| (Marghoob *et al.* 1993) | To estimate the size of the increased risk of developing a metachronous BCC in patients with a history of BCC. | Retrospective case series based on chart review of patients with a history of BCC with comparison with BCC incidence in the general population. | 260 patients with a history of BCC.<br><br>**US** | Metachronous BCC tumours. | Of the 260 patients, metachronous BCCs developed in 137 within an average of 38.3 months, a 5-year cumulative rate of one or more new BCCs of 45.2%.<br><br>The yearly risk for metachronous BCCs developing in the study population remained high during the 5-year interval.<br><br>In the general white population of the United States, the 5-year incidence of BCC was calculated to be 5% ($p < 0.005$, chi-square test).<br><br>Authors conclude that patients with a history of BCC require life-long follow-up because of the high probability of metachronous BCCs developing. | BCC tumours occurring within scars of previous BCC excision were excluded, therefore study designed to measure incidence of metachronous BCC.<br><br>BCC tumours synchronous with primary BCC were also excluded (or occurring within 2 months of primary BCC). | 3 |
| (Nixon *et al.* 1986) | To follow-up patients diagnosed with SCCs (Accuracy of diagnosis part of study not relevant to this question). | Case series. | 299 patients with 305 SCCs (genital and oral SCCs were excluded).<br><br>**Australia** | Local recurrence.<br><br>Metastasis. | Follow-up possible for 291 patients with 297 SCCs.<br><br>4 tumours metastasised (mean follow-up 37 months). Duration between excision and metastasis was 2-20 months (mean 10.3 months).<br><br>18 tumours recurred locally (mean follow-up 30.4 months). Duration between excision and recurrence was 2-24 months (mean 7.7 months).<br><br>Assuming no metastases in those lost to follow-up, there was a metastasis rate of 2% overall and 1.7% for tumours on sun-exposed areas. | On basis of results, authors suggest a follow-up of at least 2 years after treatment. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Park *et al.* 1994) | To assess the need for outpatient follow-up of patients who had a primary BCC excised. | Case series. | 206 patients with an excised primary BCC.<br><br>Follow-up varied from nil to up to 5 years.<br><br>**UK** | Clinical and histological parameters tumour size; depth; site of lesions; histology and adequacy of excision.<br><br>Local recurrence. | 14 patients lost to follow-up.<br>192 patients presented with 215 lesions.<br>Overall local recurrence rate was 5.1% with 39% of lesions recurring if the tumour was incompletely excised compared with 1% if it was excised completely. | There is lack of clarity as to whether authors include any metachronous tumours in addition to locally recurrent tumours.<br><br>Adequacy of follow-up?<br>155 patients discharged back into care of GP. Assumption made that any recurrences would have been seen by unit and thus absence of case note recurrence felt to be an accurate measure of outcome- validity?<br><br>Authors suggest that complete excision to key to surgical control and there is no need to follow-up patients routinely if the BCC has been completely excised. | 3 |
| (Rowe *et al.* 1989a) | To investigate recurrence following BCC treated with surgical excision, radiotherapy, cryotherapy, curettage and electrodessication, and Mohs micrographic surgery. | Systematic review. | **Review undertaken in the US** | Local recurrence by mode of treatment and by length of follow-up of primary studies.<br><br>Metastatic rate. | Less than one-third of all recurrences appear in the first year following treatment; 50% appear within the first 2 years following treatment; and 66% appear within the first 3 years following treatment. 18% of recurrences appear between the fifth and tenth year following treatment, irrespective of treatment modality.<br><br>Seventy-two studies reporting short-term recurrence rates (follow-up less than 5 years) had a weighted average recurrence rate of 4.2%, whereas 34 long-term studies (follow-up of 5 years) had a weighted average recurrence rate of 8.7%, or more than 2 times the short-term rate.<br><br>Five-year recurrence rates by treatment modality are as follows: Mohs | | 1+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | micrographic surgery 1.0%, surgical excision 10.1%, curettage and electrodessication 7.7%, radiotherapy 8.7%, and cryosurgery 7.5%.<br><br>The authors concluded that lifetime follow-up is necessary after treatment of primary BCC in order both recurrences and new primaries. | | |
| (Thomas *et al.* 1996) | To determine whether patients with BCCs need to be followed up and if so, for how long; which types is prone to recur and whether recurrence is related to adequacy of excision. | Case series. | 278 BCCs excised.<br><br>**UK** | Site, involvement of neighbouring structures, interval between excision of primary lesion and appearance of local recurrence; histology of primary and locally recurrent lesion and adequacy of excision margins | There were 8 recurrences.<br>No definite correlation between histological type and recurrence..<br>5 of 8 cases had been completely excised.<br><br>It took 2 years for a recurrence to appear, thereafter the frequency increased. | Recurrences or new lesions? Small numbers.<br><br>Authors conclude that all patients with excised BCC should be followed up for at least 3 years. | 3 |

## Melanoma

### The questions

*In patients with successfully treated primary melanoma, how effective is follow-up in secondary care in improving survival?*

*In patients with successfully treated primary melanoma, how effective is follow-up in secondary care in detecting recurrence?*

### The nature of the evidence

Fifteen studies were identified as follows:

- One systematic review of good quality
- One clinical guideline of good quality
- One case control study of good quality
- Eleven observational studies of fair quality
- One expert review of fair quality

Six studies originate from the UK and six are from the US. Two studies are from France and one each is from Germany and Australia. Generalisability to the UK is therefore limited. All of the studies relate to patients with melanoma.

### Summary of the supporting evidence for the recommendations

### Rate and timing of recurrence of melanoma

**There is evidence from observational studies to suggest that melanoma has capacity to metastasise, with estimates of the rate of metastatic recurrence ranging from 2.2% for primary tumours < 0.76 mm thick to 21.8% for stage I melanoma. Thicker primary tumours appear to have greater capacity to metastasise and tend to do so earlier.. Observational study evidence suggests that 2.6% of patients with melanoma develop a synchronous tumour within 2 months and 80% of metastatic tumours**

**occur within 3 years of the treatment of the initial tumour, but a small number of patients may experience metastatic recurrence 5 or 10 years after initial surgery. The same level of evidence suggests that initially diagnosed tumours are thicker, more likely to be ulcerated and have greater Clark level than metachronous tumours. Observational study evidence is not suggestive of any difference in either anatomical site of metastasis or survival between patients with late, versus early recurrence of melanoma.**

**Means of detection of recurrences**

**Physical examination and patient self examination are widely suggested in the follow-up of patients with melanoma within the studies identified, and are cited as effective methods by one systematic review. Observational studies suggest that patients detect between 47% and 72% of recurrent melanoma tumours. However there is some evidence of the same level suggestive of a five year survival advantage where recurrence was detected by a clinician. Observational study evidence suggests that doctors are able to identify smaller nodal recurrences than patients but with no survival advantage demonstrated.**

**Suggested frequency of follow-up for patients with melanoma**

**Studies vary somewhat in their recommendations for follow-up of patients with melanoma, with some studies suggesting that frequency be based upon a judgement made of widely accepted prognostic factors e.g. thickness. Observational study evidence suggests that early detection of recurrent melanoma is associated with a significant benefit in terms of overall survival. Observational studies recommend follow-up of frequency ranging from every four months to every three months for 3 years, followed by a further two annual reviews for patients with primary tumour thickness > 1.0 mm. There is some evidence of the same level that follow-up of patients with melanoma less than 0.76 mm thick is not worthwhile. French guidelines based upon a systematic review state that clinical surveillance and self-detection are indicated in all cases of**

**melanoma throughout life. Clinical guidelines produced on behalf of the British Association of Dermatologists recommend that patients with in situ melanomas do not require follow-up whereas patients with invasive melanomas should be followed up every three months for three years and that where the melanoma thickness was less than 1 mm the patient may be discharged; others should be followed up for a further two years at six monthly intervals.**

**Patients' experiences of follow-up**

**Observational study evidence suggests that whilst the majority of patients experience anxiety prior to clinic visits, they nevertheless consider follow-up to be worthwhile.**

- The case series study by Basseres et al. (1995) found that 21.8% of patients with AJCC stage I melanoma experienced subsequent metastatic disease and concluded that only clinical examination is truly cost-effective in the detection of metastases and recommended that follow-up should be undertaken 3 times a year.

- The case series study by Baughan et al. (1993) found that 20% of patients diagnosed with stage I melanoma developed metastasis and 72% of local and 47% of nodal recurrences were either symptomatic or detected initially by the patient. Doctor-diagnosed nodal recurrences were smaller and involved fewer histologically positive nodes, but subsequent survival was identical. The authors recommended that frequency of follow-up should be determined by risk, that annual follow-up should continue for 15 years and also that a clinical nurse specialist should perform follow-up. 54% of patients reported anxiety prior to clinic visits whereas follow-up was considered worthwhile by 95% of patients.

- The case series study by Brobeil et al. (1997) found that 2.6% of patients with melanoma developed a synchronous tumour within 2 months and another 44 patients (1.7%) developed a metachronous primary melanoma during the follow-up period. The initially diagnosed

tumours were significantly thicker, more likely to be ulcerated and had greater Clark level than subsequent metachronous tumours.

- The case series study by Dicker et al. (1999) found that 19% of patients with melanoma developed metastatic recurrence. 80% of recurrences were within 3 years of the initial tumour, but a small number of patients (< 8%) had recurrences 5 or 10 years after initial surgery. 47% of recurrences were discovered by patients, and only 26% were detected at a follow-up clinic. 65% had been seen within the previous 3 months. Dicker et al. (1999) recommended 3-monthly review of patients with invasive melanoma for the first 3 years with 2 further annual reviews for patients with lesions 1.0 mm or greater. Patients with in-situ lesions should be reviewed once, to confirm adequate excision and to provide education. Surveillance beyond 5 years is only justified where there are specific risk factors.

- The prospective case series by Garbe et al. 2003 found that 2.3% of patients developed second primary melanomas and that metastatic disease (including local lymph node metastases) occurred in 5.6% of patients. In stage I to III disease, physical examination discovered 50% of recurrences. 48% of metastases were classified as early detection, and these patients had a significant benefit of overall survival probability.

- The cross sectional survey by Johnson et al. (2001) found that plastic surgeons modified their follow-up practices slightly according to the patient's initial TNM stage, with significantly more frequent follow-up for increasing TNM stage.

- The case series study by Johnson et al. (1999) found the metastatic recurrence rate of melanoma to be 2.2% where primary tumours were < 0.76 mm thick (classed as thin tumours) and 12.5% for primary tumours 0.76 – 1.5 mm thick (classed as thick tumours). The mean time to metastatic recurrence was 84.5 (range 49-143) months for thin tumours and 45.3 (range 2-74) months for thick tumours. All

recurrences in the thin tumour group were widespread metastatic untreatable disease. Johnson et al. (1999) concluded that follow-up of patients with melanoma less than 0.76 mm thick is not worthwhile and provides evidence supportive of annual review for 7 years in patients with melanomas between 0.76 and 1.5 mm thick.

- The cross sectional survey by Margenthaler et al. (2003) found that the pattern of medical test utilisation in follow-up of patients with melanoma varied significantly by geographic region, with utilisation by non U.S. surgeons exceeding utilisation in any U.S. census region.

- The case series study by Moloney et al. (1996) found that following thin (<0.76mm) stage I primary melanoma, (metastatic) recurrence occurred in 24 patients (4%). Recurrences were reported as disseminated disease, nodal recurrence, metastatic skin recurrence and local skin recurrence. After 5 years follow-up, recurrences were either not surgically treatable or had poor prognosis. The authors concluded that the need for prolonged hospital follow-up of thin melanoma is questionable, suggesting instead a 2 year review policy.

- The case series study by Ruark, Shaw, and Ingvar (1993) found that following primary stage I melanoma, 72% of recurrences were detected by patients, 15% by specialists and 13% by family doctors. The individual detecting the recurrence influenced prognosis, with survival at 5 years being highest where the local doctor detected the recurrence (65%) compared with patient (42%) and specialist (39%)($p = 0.03$). There were no significant differences in 5 year survival between patient groups defined by length of follow-up received. The authors concluded that patient education is important as part of frequent follow-up.

- The case series study by Sylaidis et al. (1997) found that for patients with thick melanoma tumours (≥ 4mm) the incidence of treatable metastatic recurrences peaked in the first year of follow-up at 40% and recurrences levelled off after 5 years at 2.5% per annum. The authors suggested the need for 10-year follow-up.

- French clinical guidelines based upon a systematic review produced by Negrier et al. (2000) concluded that follow-up of patients with melanoma is based on physical examination, that patient information must encourage self-surveillance and that clinical surveillance and self-detection are indicated in all cases throughout life.

- The case control study by Pearlman et al. (1992) compared anatomical sites of metastases and survival between patients with late, versus early metastatic recurrence of disease and found that metastatic pattern and survival after relapse of disease appear to be similar for patients with early and late recurring melanoma.

- Clinical guidelines produced by Roberts et al. (2002) on behalf of the British Association of Dermatologists recommend that patients with *in situ* melanomas do not require follow-up, whereas patients with invasive melanomas should be followed up 3-monthly for 3 years. Where the melanoma thickness was less than 1 mm the patient may be discharged; others should be followed up for a further 2 years at 6-monthly intervals.

## EVIDENCE TABLE 5.2

***In patients with successfully treated primary melanoma, how effective is follow-up in secondary care in improving survival?***

***In patients with successfully treated primary melanoma, how effective is follow-up in secondary care in detecting recurrence?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Basseres *et al.* 1995) | To assess the cost-effectiveness of surveillance after resection of a stage I melanoma. | Case series. | 528 patients with stage I melanoma regularly followed up in a dermatology department 1981-1991.<br><br>**France** | Relapses (metastases). | 115 out of 528 relapsed; 33% were detected by the patient himself, 16% by the referring physician and 39% were detected in our department. Chest X-ray or abdomen ultrasonography revealed only 10% of relapses; CT scans were useless. There was a huge gap between the cost-effectiveness of clinical examinations and radiology. The time between relapse and the last check-up in the department was less than 4 months in one third of the metastases. | Authors conclude that In stage I melanoma, only clinical examination is cost-effective in the detection of metastases. However, many metastases are likely to become prominent between two examinations if patients are examined less than 3 times a year. A progressive decrease in frequency is thus not advisable, until the risk is considered low enough to stop follow-up. | 3 |
| (Baughan *et al.* 1993) | To assess the value of a single dedicated clinic to perform follow-up of patients with melanoma in diagnosing and treating tumour relapse and its value as | Case series. | 331 patients with stage I melanoma.<br><br>**UK** | Metastatic rate, reported as patients' perceptions of clinic. | 65 (20%) have developed tumour recurrence. Fifty-five first relapses were either local or in regional lymph nodes and thus potentially curable; half were found within 3 months of the previous clinic visit. 72% of local and 47% of nodal recurrences were either | Authors suggest that study demonstrates that he clinic makes inefficient use of medical time. Routine follow-up examinations should be performed by a clinical assistant or a clinical nurse | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | perceived by patients. | | | | symptomatic or detected initially by the patient. Doctor-diagnosed nodal recurrences tended to be smaller and to involve fewer histologically positive nodes, but subsequent survival was identical in those with patient-diagnosed nodal recurrences.<br><br>54% of patients suffer anxiety prior to clinic visits. Follow-up was considered worthwhile by 95% of patients and regular visits were preferred to a 'walk in' system. | specialist.<br><br>Other recommendations include:<br>• frequency of follow-up should be increased for patients at high-risk of relapse and a strategy is suggested dependent on ulceration, stage, thickness<br>• annual follow-up should continue for 15 years. | |
| (Brobeil *et al.* 1997) | To determine the impact of an intensive follow-up protocol on the stage of disease at diagnosis of subsequent primary melanomas. | Case series. | 2,600 consecutively registered melanoma patients.<br><br>**US** | Tumour thickness, Clark's level, ulceration. | 67 patients (2.6%) had another synchronous melanoma diagnosed at the time of presentation to the clinic or within 2 months and another 44 patients (1.7%) developed a 2nd metachronous primary melanoma during the follow-up period.<br><br>For the 44 patients diagnosed with metachronous lesions, the mean tumour thickness for the first invasive melanoma was 2.27 mm compared with 0.90 mm for the second melanoma. The first melanomas diagnosed were thicker by an average of 3.8 mm ($p = 0.008$).<br><br>The mean Clark level for the initial melanoma was greater than the mean level for subsequently diagnosed melanomas ($p = 0.002$).<br><br>23% of the initial melanomas were ulcerated, whereas only 1 of the 2nd primary lesions were ($p = 0.002$). | Cannot declare a causal link between 2nd lesions being "better" than 1st and the follow-up programmes. | 3 |
| (Dicker *et al.* 1999) | To evaluate 5-year follow-up in patients with melanoma. | Case series; cross-sectional survey. | 1568 patients on SE Scotland melanoma database with stage 1 melanoma excised1979-1994. | Recurrence; method of detection; patient practices. | 293 (19%) developed a metastatic recurrence, 32 had a 2nd primary melanoma (metachronous tumour) and 97 had an in-situ melanoma. Disease-free interval shortened progressively | Authors recommend 3-monthly review of patients with invasive lesions for the first 3 years. Then, those with lesions >/= 1.0 mm need 2 | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | **UK** | | with increasing tumour thickness. 80% of recurrences were within 1st 3 years, but a few patients (< 8%) had recurrences 5 or 10 years after initial surgery. In-situ melanomas did not recur.<br><br>47% of recurrences were noted 1st by patients, and only 26% were detected 1st at a follow-up clinic. 89% were still under review when their recurrences were detected, and 65% had been seen within the previous 3 months.<br><br>Questionnaires were completed by 120 patients: sun protection and avoidance, and mole examination were more likely after melanoma excision. | further annual reviews. Patients with in-situ lesions should be reviewed once, to confirm adequate excision (0.5 cm margins) and to give appropriate education. Surveillance beyond 5 years is only justified if there are special risk factors. | |
| (Garbe *et al.* 2003) | To prospectively examine and evaluate the results of follow-up procedures in a large cohort of cutaneous melanoma patients. | Prospective case series. | 2,0008 consecutive patients with stage I to IV melanoma 1996-1998.<br><br>**Germany** | Follow-up examinations and data: demographics, tumour characteristics, clinical or technical examinations performed. Detection of metastases; survival probabilities. | A total of 3,800 clinical examinations and 12,398 imaging techniques were documented. 62 second primary melanomas in 46 patients and 233 metastatic disease recurrences in 112 patients were detected during this time. In stage I to III disease, physical examination was responsible for the discovery of 50% of all metastatic recurrences. In the primary tumour stages, 21% of all recurrences were discovered by lymph node sonography, with the majority being classified as early detection. 48% of the recurrences were classified as early detection, and these patients had a significant benefit of overall survival probability. | Authors suggest that an elaborated follow-up schedule in cutaneous melanoma is suitable for the early detection of second primary melanomas and early recurrences. The intensity of clinical and technical examinations can be reduced during follow-up of patients in the primary tumour stages and may be intensified in locoregional disease.<br><br>Recommended follow-up strategy dependent on stage, thickness suggested involving frequency and tests to be performed. | 3 |
| (Johnson *et al.* 2001) | To evaluate the effect of TNM stage on the self-reported surveillance strategies employed by practicing plastic surgeons caring for otherwise healthy | Cross-sectional survey, using hypothetical scenarios. | A random sample (N=3,032) of the 4,320 members of the American Society of Plastic and Reconstructive Surgeons. | The effect of TNM stage on the surveillance strategies. | Surveillance of patients after resection of melanoma relies mostly on office visits, chest X-ray, CBC, and liver function tests. All other surveillance modalities are used infrequently. Most respondents modify their surveillance practices slightly according to the | 35% response rate (same study population as Margenthaler paper). | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | patients subjected to potentially curative treatment for cutaneous melanoma. | | **US** | | patient's initial TNM stage. Most commonly used modalities are employed significantly more frequently with increasing TNM stage. This effect persists through ten years of follow-up, but the differences across stages are tiny. | | |
| (Johnson *et al.* 1999) | To determine the value of follow-up in two subgroups of patients with a thin melanoma less than 0.76 mm and 0.76-1.5 mm thick. | Case series. | 306 patients presenting to a melanoma clinic 1976 – 1994 Group 1: Thinner than 0.76mm = 178; Group 2: 0.76-1.5mm = 128 Length of follow-up (mean 88.6 (range 4-296) versus 80.4 (range 2-296) months).<br><br>**UK** | Recurrence. | Four patients (2.2 per cent) developed recurrence in group 1 and 16 (12.5 per cent) in group 2. The mean time to recurrence was 84.5 (range 49-143) months in group 1 and 45.3 (range 2-74) months in group 2. All 4 patients in group 1 and 14 of 16 in group 2 died from recurrent disease.<br><br>All patients with recurrent disease in group one (thinner primary tumours) had widespread metastatic disease.<br><br>Recurrence in group two (thicker primary tumours) included local, subcutaneous, in-transit, nodal and distant recurrences. | Authors conclude that follow-up of patients with a melanoma less than 0.76 mm thick is not worthwhile. All recurrences would have been detected by annual review for 7 years in patients with melanomas between 0.76 and 1.5 mm thick. | 3 |
| (Johnson *et al.* 2004) | To clarify and update workup and follow-up strategies based on fundamental principles and current data and to discuss new and current concepts regarding sentinel lymph node biopsy (SLNB), particularly in relation to the staging workup. | Review/discussion. | Studies pertaining to staging workup, SLNB and follow-up tests.<br><br>**US** | Unclear. | Routine tests have marginal to no efficacy and are not cost-efficient for detecting occult disease in asymptomatic patients with localised melanoma. The only **staging** test that has relatively high sensitivity and specificity and provides tissue diagnosis is SLNB. | Methodology not described. | 4 |
| (Margenthaler *et al.* 2003) | To investigate whether geographical factors account for variation in post treatment melanoma surveillance intensity among plastic surgeons. | Cross-sectional survey. | Random sample (n=3,032) of the 4,320 members of the American Society of Plastic and Reconstructive Surgeons (ASPRS). | Practice patterns relating to 14 specific follow-up modalities correlated with TNM stage, year post surgery, U.S. | Correlation analysis showed that mean follow-up intensity for the modalities surveyed was highly correlated across TNM stages and years post surgery. Within MSAs, only chest radiograph utilisation varied significantly. The pattern of testing varied significantly by | 35% response rate (same study population as Johnson and other Margenthaler papers). | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | **US** | census region, metropolitan statistical area (MSA), and managed care organisation (MCO) penetration rate. | geographic region for 7 modalities (office visit, computed tomography scan of the brain and chest/abdomen, alpha-fetoprotein level, 5S-cysteinyl dopa level, abdominal ultrasonogram, bone scan); in each of these, utilisation by non-U.S. surgeons exceeded utilisation in any U.S. census region. The pattern of testing varied significantly by MCO penetration rate for chest radiograph (greater utilisation in the lowest MCO penetration rate areas) and 5S-cysteinyl dopa level (greater utilisation in the highest MCO penetration rate areas). | | |
| (Moloney *et al.* 1996) | To identify recurrence rate of thin melanomas; to assess contribution of surgical follow-up to recurrence detection; to assess effectiveness of long-term hospital follow-up. | Case series. | 602 patients with minimum follow-up of 5 years with thin (<0.76mm) stage I melanoma excised 1967-1989.<br><br>**UK** | Recurrences, reported as disseminated, nodal, skin metastases and local skin recurrence. | Recurrence occurred in 24 patients (4%); 5 surgically treatable recurrences (< 1%) occurred within 5-years following surgery. After 5 years there were 4 surgically treatable recurrences, (with poor prognosis) and 6 cases which were not surgically treatable. | Authors question the need for prolonged hospital follow-up of thin melanoma – a 2-year review policy would have detected all 4 tumours in which further surgery resulted in >5-year survival. | 3 |
| (Negrier *et al.* 2000) | To provide evidence based clinical guidelines for clinicians in the diagnosis, treatment and follow-up of patients with cutaneous melanoma. | Clinical guidelines underpinned by systematic review with peer review undertaken by panel of experts. | Patients with melanoma.<br><br>**France** | Outcomes are research findings to inform practice based upon systematic review. | The recommendations are summarised as: 1) The primary prevention of melanoma is based on a reduction in exposure to ultraviolet rays (solar or artificial). 2) The diagnosis of melanoma requires the surgical removal and histological examination of the lesion. 3) The pathological report must include the diagnosis of primary malignant melanoma, the maximum thickness of the tumour in millimetres (Breslow), the clearance of surgical margins, the level of invasion (Clark), the presence and extension of regression and the presence of any ulceration. 4) The standard treatment of a primary melanoma without lymph node involvement is based on surgery that must ensure adequate margins depending on the thickness of the tumour. 5) After surgery of a stage I | Systematic review which underpins guidelines not seen. Information provided in methodology section sufficient to permit appraisal with AGREE instrument and to accept as high level evidence. | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | melanoma, there is no indication for additional treatment outside a prospective therapeutic study. 6) For a local recurrence without node involvement, in the absence of other metastases, surgical excision is the standard treatment. 7) In the case of metastatic regional lymph nodes, a complete regional lymphadenectomy is required. There is no indication for additional treatment outside a prospective therapeutic study. The inclusion of these patients in controlled studies of immunotherapy is recommended. 8) There is no standard therapeutic strategy for metastatic melanoma. Conventional palliative treatment is chemotherapy with dacarbazine. 9) Follow-up is based on physical examination. Patient information must encourage self-surveillance. Clinical surveillance and self-detection are indicated in all cases throughout life. | | |
| (Pearlman *et al.* 1992) | To compare recurrence sites and subsequent survival in patients with melanoma. | Case-control study. | Cases:<br>35 patients with disease-free intervals 72-240 months (median: 127 months)<br>Controls:<br>35 patients with disease-free intervals 4-56 months (median:26.7 months).<br><br>**US** | Distribution of metastatic recurrence sites; survival. | Distribution of metastatic recurrence sites in early relapse:<br>66% in regional nodes or soft tissue;<br>34% in distant soft tissue or viscera.<br><br>Distribution of recurrence sites in late relapse:<br>49% in regional nodes or soft tissue;<br>51% in distant soft tissue or viscera (no significant differences).<br><br>Median survival for patients with early and late metastases in regional nodes or soft tissue was 26 and 44 months, respectively (no significant differences); 5-year survival was 27% and 33%, respectively (no significant differences). Median survival was similar for early or late relapse in distant soft tissue or | Appears that metastatic pattern and survival after recurrence are similar for patients with early and late recurring melanoma.<br><br>Not all cutaneous melanoma – some ocular.<br><br>Small numbers. | 2- |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | viscera (8 and 10 months, respectively), as was 5-year survival (0% and 6%, respectively). | | |
| (Roberts *et al.* 2002) | To provide evidence based recommendations treatment of patients with melanoma. | Evidence based guidelines, with recommendations graded according to the quality of evidence available. | Patients with melanoma.<br><br>**UK** | Guidelines discuss available studies and draw up recommendations based upon studies or upon expert consensus where evidence is insufficient. | Recommends:<br><br>Patients with in situ melanomas do not require follow-up.<br><br>Patients with invasive melanomas should be followed up 3-monthly for 3 years. Where the melanoma thickness was less than 1 mm the patient may be discharged; others should be followed up for a further 2 years at 6-monthly intervals. | 60 references cited.<br><br>Scale for strength of evidence and grade of recommendations included. | 4 ++ |
| (Ruark *et al.* 1993) | To determine whether the source identifying the recurrence impacts overall survival, thereby potentially influencing the frequency of follow-up. | Case series. | 2268 patients with stage I melanoma treated 1980-1986.<br><br>Median follow-up period was 52 months (range not given).<br><br>**Australia** | Recurrence, method of detection; site of recurrence; 5-year survival, overall survival. | Recurrence detected in 411 patients.<br>Method of detection only recorded in 257 cases:<br>Patient detected 72%<br>Specialist doctor 15%<br>Local doctor 13%<br>Overall 5 year survival was 45%<br>Median time interval to 1st recurrence was 17 months (range 1-99 months)<br>Comparison of groups based on place of treatment and subsequent follow-up revealed no significant differences in sex, tumour depth, primary site, recurrence interval or length of follow-up.<br>Pattern of recurrence site differed in that loco-regional recurrence was seen more frequently in group treated elsewhere ($p = 0.01$).<br>Factors influencing prognosis included: gender ($p = 0.014$); tumour depth ($p = 0.04$), site of first recurrence ($p = 0.0001$) and who noted recurrence ($p = 0.03$).<br>Survival rates at 5 years when recurrence detected by patient, melanoma specialist or local doctor were 42%, 39% and 65% respectively. | Authors conclude that patient education in addition to frequent medical follow-up appears essential in detection of early recurrence which ultimately influences survival. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Differences in overall survival were not significant based on place of treatment or follow-up. | | |
| (Sylaidis *et al.* 1997) | To determine follow-up requirements for patients with thick melanoma in terms of surveillance ad frequency of reviews. | Case series. | 244 patients with melanoma>/= 4mm followed-up for 10 years or who had died of melanoma within 10 years.<br><br>**UK** | Recurrences; reported as local, regional or distant.<br><br>Survival. | 5-year survival 45% (95% CI 39-51%)<br>10-year survival 37% (95% CI 31-43%)<br>Incidence of treatable recurrences peaked in 1st year at 40%.Recurrences levelled off after 5 years at 2.5% per annum. | Authors suggest need for 10-year follow-up. Strategy suggested based on annual risk of getting a recurrence:<br>Year Frequency<br>1 2-monthly<br>2 3-monthly<br>3 4-monthly<br>4 5-monthly<br>5-10 6-monthly<br>>10 12-monthly<br>>10 reviews done by GP. | 3 |

## Patient self examination

### The questions

*In the follow-up of patients with skin cancer, what is the usefulness of education for self examination?*

### The nature of the evidence

Twelve papers were identified representing eleven studies (with one RCT reported at two stages of follow-up) as follows:

- One RCT of good quality
- One systematic review of good quality
- One case control study of good quality
- Eight observational studies, four of good quality, one of fair quality and three of poor quality

Only one study originates from the UK. Seven studies are from the US, one study is from Australia and two studies are from Italy. Generalisability to the UK is therefore limited.

Seven studies are of patients at risk of melanoma based upon family history or presence of naevi. Three studies are of screened populations and two studies are of patients with proven melanoma.

### Summary of the supporting evidence for the recommendations

### Self examination (SE) versus physician examination

**There is consistent evidence that expert physician examination has greater reliability than SE in detecting melanoma. Systematic review evidence suggests that melanoma lesions detected by physicians are thinner than those detected by patients. Observational study evidence suggests that detection by dermatologist is associated with earlier melanoma diagnosis and that input by physicians is the strongest single**

**determinant of SE, although there is little evidence for improved survival arising from recurrences of melanoma diagnosed by patients compared to recurrences diagnosed by hospital doctors. The same level of evidence suggests that SE based on naevi count has poor concordance with dermatological assessment for risk of melanoma and is not reliable.**

**Factors affecting SE**

**Studies have identified a number of patient characteristics and also events which are associated with SE. Systematic review evidence suggests that elderly men have lower rates of SE. There is observational study evidence that factors associated with greater likelihood of patients performing self skin examination are:**

- **skin awareness**
- **habitual sun protection**
- **previous benign skin biopsy**
- **family cancer history**
- **personal history of skin cancer**
- **physician or nurse examination or recommendation**
- **help from a spouse (especially wives assisting husbands)**
- **presence of a wall mirror**
- **age <50 years**

**The same level of evidence suggests that older patients may be less likely to perform SE.**

**Rates of SE**

**Estimates of rates of SE vary widely within the studies identified, according to factors such as populations studied and different**

**definitions of SE or questions used by researchers to ascertain rates of SE. Subsequently, estimates of rates of SE from observational studies have range 9% to 87%. A rate of 71.6% for SE performed within the preceding year, was reported amongst first degree relatives of melanoma patients by Manne et al., (2004). Systematic review evidence suggests that the effect of promoting SE cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons. RCT and case control study evidence suggests that rates of SE can be significantly improved through educational interventions.**

**Role of photography in SE**

**Evidence from one RCT suggests that the use of photography as an adjunct to health education produces no short term (i.e. same day as intervention) difference in compliance above standard education for SE but the same level of evidence is suggestive of a four month follow-up advantage in terms of rate of SE through the use of photographs.**

**Benefit of SE**

**Case control study evidence suggests that SE is associated with a marginally significant reduced risk of melanoma incidence: OR 0.66 [95% CI 0.44-0.99] which is reportedly an inexpensive screening method. Observational study evidence suggests that female sex, high educational level and performance of SE are associated with thinner melanoma tumours.**

- The prevalence study by Aitken et al. (2004) found that 25.9% of randomly selected adults reported whole body SE within the last 12 months and 1055 (33.9%) within the last 3 years and concluded that input by physicians is the strongest single determinant of SE.

- The case control study by Berwick et al. (1996) found that SE was performed by 15% of all subjects (patients with melanoma and population matched controls) and was associated with a marginally

significant reduced risk of melanoma in all subjects: OR 0.66 [95% CI 0.44-0.99].

- The qualitative study by Berwick et al. (2000) found that amongst a sample of patients with a history of melanoma and also lower risk patients without a history of melanoma, the rate of reported SE was 32% at baseline, rising to 64% after an educational intervention (p = 0.03).

- The survey of patients referred by their GPs to a pigmented lesion clinic undertaken by Carli et al. (2002) found poor concordance between SE and dermatological assessment for both common and atypical naevi and concluded that SE of melanoma risk is not reliable.

- The case series study by Carli et al. (2003) found that 40.6% of patients with melanoma sampled self detected their melanoma tumour. Female sex (OR 0.70 [95% CI 0.50-0.97]), high educational level (0.44 [95% CI 0.24-0.79]) and performance of SE (0.65 [95% CI 0.45-0.93]) were factors associated with thinner tumours. 48% of patients performed SE, but only 20.4% regularly.

- The systematic review by Helfan et al. (2001) found melanoma lesions detected by physicians to be thinner than those detected by patients. Elderly men had lower rates of SE and the authors recommended that physicians perform skin examination in these patients. The authors reported that the effect of promoting SE cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons.

- The qualitative survey of first degree relatives of patients with melanoma by Manne et al. (2004) found the rate of SE in the last year to be 71.6%. SE correlated closely with having received a clinical skin examination by a physician.

- The case series study of patients with metastatic melanoma by Odili and Evans (2001) found that 56% of cases of recurrent melanoma

were patient detected and no significant difference in survival between recurrences diagnosed by SE and those diagnosed by hospital doctor were found.

- The qualitative study by Oliveria et al. (1999) found that amongst a sample of Caucasian people without melanoma, skin awareness was a strong factor associated with SE whereas older age and higher education was associated with a decreased likelihood of performing SE.

- The RCT by Phelan et al. (2003) compared nurse education for SE and provision of skin photographs with nurse education and provision of standard brochure in patients with 5 or more dysplastic naevi, with or without a history of melanoma. The mean group scores for knowledge, awareness and confidence increased in both groups at immediate follow-up ($p < 0.0001$) but there were no significant differences in scores between the photography group and the brochure group.

- The RCT of patients at high risk for melanoma based upon dysplastic naevi by Oliveria et al. (2004) provided further follow-up to the study by Phelan et al. (2003) and found that a teaching intervention with photo book demonstrated a 51% increase in 3 or more reported examinations at 4 month follow-up, compared to a 17.6% increase in the group which received teaching only [$p = 0.001$].

- The observational pilot study (as part of a subsequent trial) by Weinstock et al. (2004) found the rate of SE amongst patients attending for routine follow-up visits to be between 12% and 38%. Help from a partner and presence of a wall mirror were associated with higher rates of SE whereas visual impairment was found to be associated with lower rates of SE.

# EVIDENCE TABLE 5.3

## *In the follow-up of patients with skin cancer, what is the usefulness of education for SE?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Aitken *et al.* 2004) | To establish the prevalence and determinants of self skin examination (SE) in a high risk population. | Prevalence study based upon sample of adults randomly sampled and interviewed by telephone. | 3110 adult residents of Queensland aged 30 years or more.<br><br>**Australia** | OR of SE based upon investigated factors, analysed in univariate regression and for those found to be significant by this method, multivariate regression. | 804 (25.9%) participants reported whole body SE within the last 12 months and 1055 (33.9%) within the last 3 years. Whole body SE was associated in multivariate analysis with age <50 years, higher education, examination/advice by physician, regarding skin checks a priority, concern about skin cancer and personal history of skin cancer. Author concludes that input by physicians was the strongest single determinant of SE and that this should increase in primary practice, targeting people at highest risk and older people. | Study undertaken as preparatory work for a large, community based RCT. Of 9211 contacts, 4999 ineligible, 987 refused, 115 interviews incomplete, leaving 3110 complete interviews. Demographic details of subjects described.<br><br>Provides a summary of 13 other studies assessing the prevalence of skin SE. Estimates vary widely, according in part, to how the question on SE is poised (range 9% to 87%). | 3++ |
| (Berwick *et al.* 1996) | To determine whether early recognition of melanoma through skin SE is associated with a decreased risk of lethal melanoma (i.e. death from melanoma or development of distant metastases). | Case control study: 650 cases (Caucasian patients with primary melanoma) and 549 Caucasian population controls selected randomly and age-sex frequency matched with cases. | Connecticut residents (cases = patients with primary melanoma stage I to III).<br><br>**US** | OR of melanoma quoted for SE and confounding variables in multivariate analysis. Separate estimation of primary and secondary prevention obtained. | SE was practised by 15% of all subjects and was associated with a marginally significant reduced risk of melanoma in all subjects: OR 0.66 [0.44-0.99] (primary prevention). Risk of advanced disease in melanoma cases was reduced by SE, but this was not found to be significant (secondary prevention, OR 0.58 [0.31-1.11]) Author concludes SE can reduce new incidence of melanoma. | Mean follow-up 5.4 years. Author acknowledges possible lead time bias to affect estimate of secondary preventive impact. | 2 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Berwick *et al.* 2000) | To determine factors important to the design of a nurse education intervention to increase the frequency of SE practices. | Pilot (qualitative) study measuring SE pre and 18 month post educational intervention (with concurrent clinical examination, photography and treatment where necessary). | 75 subjects: 60 High risk patients (i.e. history of melanoma [37], atypical naevi [23]) attending a pigmented lesion clinic and 15 low risk subjects (with neither melanoma history nor atypical naevi) sourced from a different study.<br><br>**US** | Reported change in SE practice and tested knowledge of melanoma after intervention compared to baseline. Optimum SE defined as one to two monthly. | Pre intervention SE was 32%. Reported SE did not vary by risk group at baseline. 27% of subjects reported SE daily/weekly i.e. too frequently to be effective. Post intervention SE doubled to 64%: a significant change (p = 0.03). Of these 29% conducted full SE and 61% conducted partial SE. Author concludes that performance of SE correlates with nurse/physician recommendation. | Pilot study has low power and limited applicability due to recruitment method. Low risk group was older and (significantly) more highly educated than high risk group. | 3 - |
| (Carli *et al.* 2002) | To investigate the melanoma detection rate in accordance with cause of referral to a Pigmented Lesion Clinic (PLC) and also the ability of patients to classify their melanoma risk based upon self counting of naevi. | Survey of 204 patients seen at a single PLC over a one month period. Patients were questioned by questionnaire. Patients self counted their normal and atypical naevi, for comparison with the assessment by the dermatologist. | Patients referred to PLC by family doctor.<br><br>**Italy** | Sensitivity, specificity, PPV and NPV. Concordance between self counting and dermatological assessment using chance corrected k value. | 193 questionnaires were completed. Suspicious lesions were confirmed by dermatologist in 13 of 193 patients referred by GPs. GP referral for suspicious lesion showed sensitivity 53.8%, specificity 61.1%, PPV 9.1% and NPV 94.8% using dermatological assessment as gold standard . Compared with histopathology as gold standard, PPV was 3.8% and NPV 100%. There was poor concordance between SE and dermatological assessment for both common and atypical naevi. Author recommends that GP filtering of suspicious naevi be improved. Author concludes that self assessment of melanoma risk is not reliable. | Uses number of naevi as a significant risk factor for people with Mediterranean skin type. No CI or p values provided for sensitivity etc. | 3 + |
| (Carli *et al.* 2003) | To investigate patterns of detection and variables associated with early diagnosis of melanoma in a population of intermediate risk. | Case series of 816 patients with melanoma treated at 11 centres. Patients received a questionnaire and were dermatologically examined. Multi variable analysis performed. | White people in Italy with histologically confirmed melanoma, post initial excision.<br><br>**Italy** | Main outcome measure is relationship between patterns of detection and patient/physician delay. Melanoma thickness is presented as a binary variable. OR for detection of | 331 patients (40.6%) self detected melanoma. 12.5% were detected by spouses and 38.7% by physicians. Female sex (OR 0.70 [0.50-0.97]), high educational level (0.44 [0.24-0.79]) and performance of SE (0.65 [0.45-0.93]) were associated with thinner tumours. 48% of patients performed SE, but only 20.4% regularly. When adjusted for these variables, detection by dermatologist was associated with early | Patient characteristics described. | 3+ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | lesion > 1mm thickness is used. | diagnosis (OR 0.45 [0.28-0.73]. Author concludes: patterns of detection in Mediterranean population is similar to studies of fair skinned people and supports role of SE and recommends total skin examination by dermatologists be performed to identify suspicious lesions. | | |
| (Helfan *et al.* 2001) | To examine published data on the effectiveness of routine screening for skin cancer by a primary care provider, as part of an assessment for the US Preventative services Task Force. | Systematic review looking primarily at screening, but with findings on skin SE. | Numerous populations with skin cancer or risk factors for skin cancer (various races and ages), excluding familial atypical mole and melanoma syndrome.<br><br>**US** | Outcome measures were timing of diagnosis (BCC and SCC), thickness at diagnosis (melanoma), patient knowledge and SE skills and harmful effects of screening. PPV and likelihood ratios calculated from original studies. | With regard to SE, author cites studies which imply: i) elderly men have lower rates of SE. ii) physician examination may be more effective in elderly men. iii) the effect of promoting SE cannot be distinguished from that of routine screening in patients seeing the physician for unrelated reasons. iv) melanoma lesions detected by physicians are thinner than those detected by patients. | Also cites Berwick et al. (1996) - see individual entry. Author reports evidence quality of original studies as poor. | 2+ |
| (Manne *et al.* 2004) | To examine sun protection behaviours, extent of skin examination by self and practitioner and associated psychological and non psychological factors amongst first degree relatives of individuals with melanoma. | Qualitative study of 229 subjects surveyed by telephone questionnaire. Skin examinations assessed were total cutaneous examination by a healthcare provider (TCE) and SE. | First degree relatives (aged 20 or older with no personal history of melanoma or dysplastic naevi) of individuals diagnosed with melanoma.<br><br>**US** | Numerous qualitative scores measured. | 55% of family members reported ever having TCE and reporting of engagement in SE in the last year was 71.6%. TCE and SE were closely correlated ($p < 0.001$) Physician recommendation correlated well with TCE, SE and habitual sun protection. Author concludes: interventions to improve risk reduction practices should target non psychological factors, psychological factors and physician influence. | Non English speaking people ineligible. 229 relatives fully evaluated out of 356 eligible relatives. Non participants found to be similar to participants. Statistical methods took account of numerous relatives from same families. | 3 |
| (Odili & Evans 2001) | To investigate how detection of recurrences affects overall survival. | Case series. | 73 patients with melanoma who had undergone groin or axillary lymph node dissection for recurrent disease.<br><br>**UK** | Method of detection of recurrence; survival. | Self-referral 41<br>GP 5<br>Outpatient follow-up 27<br><br>No significant difference in survival between recurrences diagnosed by self-examination and those diagnosed by hospital doctor. | Teaching of self-examination for recurrences deemed worthwhile.<br><br>No details given on how survival rates calculated. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Oliveria SA *et al.* 1999) | To investigate demographic, phenotypic, behavioural, educational and cancer history factors associated with skin SE. | Personal interview of 549 Connecticut Caucasian residents recruited as controls in a previous study (frequency matched by age/sex to mirror expected melanoma cases). | Sample of Caucasian people without melanoma.<br><br>**US** | OR of each investigated variable used with CI. Univariate and multivariate log regressions performed. | Skin awareness was a strong factor associated with skin self-examination for both females and males. For females, previous benign biopsy or the presence of an abnormal mole was identified as important for future skin self-examination using our criteria. A family history of cancer, physician examination, and change in diet to reduce cancer risk increased the likelihood of skin self-examination in males but not females. In women, light hair colour may increase the likelihood of performing skin self-examination. Older age and college or postgraduate education was associated with a decreased likelihood of performing skin self-examination in both males and females. Author concludes: Identifying factors associated with skin self-examination will enable healthcare providers to target individuals who may not be performing skin self-examination but who are at increased risk for developing melanoma. | Recruitment dependent upon previous study. Study population is not true population based sample. Several associations in 'results' based upon univariate analysis were not significant in multivariate analysis. | 3- |
| (Oliveria *et al.* 2004) | To investigate the value of i) formal patient training in SE by nurses and ii) provision of baseline photographs to patients to assist SE. | RCT using teaching intervention with photo book vs. teaching intervention with no photo book. Patients stratified according to history of skin cancer (Y/N) prior to randomisation. | Patients at high risk for melanoma attending a single pigmented lesion clinic i.e. aged ≥18 with 5 or more atypical or dysplastic naevi.<br><br>**US** | Questionnaire measured practice of SE at baseline, immediately post session and at 4 months follow-up.<br><br>Outcome measure = proportion of patients reportedly performing SE at least 3 times in the last 4 months. | Teaching plus photo group showed 51% increase in 3 or more reported examinations at 4 month follow-up, vs. 17.6% increase in teaching only group [p = 0.001]. Author concludes: Nurse led intervention increases patient adherence with SE and this is further enhanced by provision to patients of digital photos as an adjunct. | Patients excluded who were visually or physically impaired or who had been previously photographed. 100/105 eligible patients participated.<br><br>Follows prior paper on this study by Phelan et al., 2003 – wherein control group patients were also initially photographed and given photo books at 4 month follow-up point. | 1+ |
| (Phelan *et al.* 2003) | To test whether the addition of a photo book (as part of nurse led SE instruction) would assist and improve patients' SE | RCT comparing nurse education with photo book (intervention group, n= 49) with nurse | 100 high risk patients with 5 or more dysplastic naevi, with or without a history of | Measures are mean group scores for knowledge, awareness and confidence in | Patients' reported routine SE at baseline was 10% (intervention group) and 20% (control group). Mean group scores for knowledge, awareness and confidence increased in both groups at immediate | Follow-up undertaken at 'intervention' visit i.e. immediately post intervention. Further follow-up at 4 and 18 months to be reported in | 1 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | performance, knowledge, skills, awareness and confidence. | intervention with standard brochure/diary (control group, n=51). | melanoma.<br><br>**US** | performing SE, ascertained by questionnaire at baseline and immediately post intervention. | follow-up ($p < 0.0001$) but there were no significant differences in scores between groups. Author concludes that education can increase compliance with SE and (nevertheless) that photographic records may be the most effective aid for detecting changes at longer intervals. | future studies. Use of photos were not found to be more effective than use of standard brochure/diary at this stage of follow-up and 'control' group received photo books 4 months subsequently.<br><br>4 month follow-up reported in Oliveria et al., 2004. | |
| (Weinstock *et al.* 2004) | To examine the association of key characteristics of patients and their circumstances with (clearly defined a priori) thorough SE. | Preliminary study of 2126 patients interviewed using baseline telephone interviews prior to randomisation as part of a different trial. | Patients attending for routine visits with physicians working at participating practices within the *Check It Out* randomised trial.<br><br>**US** | Outcomes of interest are frequency and thoroughness of SE and characteristics related to TSSE. | 18% of participants performed TSSE as defined a priori, but other definitions led to estimates of between 12% and 38%. Help from a partner was strongly associated with TSSE, especially wives assisting their husbands. Presence of a wall mirror was an important predictor of TSSE performance and visual impairment affected performance. Author concludes: Estimates of TSSE vary substantially according to questions used by researchers to elicit responses. Study findings may be used to increase TSSE performance with the aim of reducing melanoma mortality. | Sample size based upon power calculation. Study includes subjects in addition to the 1356 who participated in the randomised trial. | 3+ |

# Chapter 6 – Management of special groups of patients with skin cancer

## Genetic predisposition to melanoma

### The question

*What are the needs of individuals at increased familial risk of melanoma?*

### The nature of the evidence

Ten studies were identified as follows:

- One systematic review and meta-analysis of good quality
- Two case control studies of good quality
- Five observational studies, one of good quality and four of poor quality
- Two expert reviews of good quality

Four studies are from the UK and one study is from the US. One study is from an international collaboration and the remaining studies were undertaken in Sweden, Germany, Denmark and jointly, in Italy and France. Applicability to the UK is reasonable, but limited.

Two studies compare samples of patients with melanoma with population based controls. Five studies identify individuals or families in whom either elevated numbers of common or atypical naevi are present, or in whom there is a familial history of melanoma. The remaining three studies are of individuals with congenital melanocytic naevi.

### Summary of the supporting evidence for the recommendations

### Individual and familial risk factors for melanoma

**Evidence from a high quality meta-analysis suggests that individuals with 101-120 common naevi are at over 6 times the risk of developing melanoma compared to those with less than 15 common naevi. The same level of evidence suggests that individuals with 5 atypical naevi are at over 6 times the risk of developing melanoma compared to those with none.**

**A consensus statement from the Melanoma Genetics Consortium reports that less than 1-2% of melanoma cases are thought to be attributable to mutations of melanoma susceptibility genes (CKKN2A and CDK4). 20 - 40 % of families in which 3 or more family members have melanoma show inheritance of mutations in the CDKN2A gene. Many aspects of genetic mechanisms are not fully understood e.g. penetrance. High familial risks for melanoma include:**

- **Multiple affected family members (RR 35 - 70)**
- **Previous primary melanoma (RR 8.5)**
- **One or more affected first degree relatives (RR 2 - 3)**
- **Multiple / atypical moles (RR 2 - 12)**
- **Fair skin (RR 1.4)**
- **Freckling (RR 2 - 3)**
- **Blue eyes (RR 1.6)**
- **Red hair (2.4 - 4)**
- **History of blistering sunburn (RR 2 - 3)**

**Observational study evidence suggests that of the melanoma types, superficial spreading melanoma shows the highest familial risk. There is equal risk of melanoma in individuals with either a sibling or parent affected with melanoma and highest risk where two offspring and a parent are affected.**

**Case control study evidence suggests that melanoma cases are significantly more likely to exhibit atypical naevi than controls, with naevi ≥2 mm sometimes exceeding 100 or more in number. Atypical mole syndrome (AMS) phenotype has been shown to be strongly predictive of an increased risk of melanoma outside the familial context and AMS phenotype is likely to be a continuous phenotype. Melanoma is associated with naevi on sun exposed and non sun exposed areas.**

**Expert review evidence suggests that 'carriers' of CDKN2 mutation have a greater number of total naevi and a higher atypical naevi score. AMS score varies across melanoma patients and within families, supporting variability of phenotype expression. The authors of one expert review recommend that all members of families with the CDKN2 mutation should be considered as potential carriers with increased risk for melanoma, since there is variation within families.**

**Recommended management of genetically predisposed individuals from the Melanoma Genetics Consortium includes education for sun protection and self examination and appropriate dermatological examination commencing from 10 years and when naevi are unstable e.g. puberty, pregnancy. Routine surgical removal of pigmented lesions is not recommended except where melanoma is suspected.**

**Atypical naevi / host factors / familial risk**

- A case control study by Bataille et al. (1996) found that the OR for presence of 4 or more atypical naevi versus one in melanoma cases: controls was 28.7 (95% CI 8.6 - 95.6, p < 0.0001). The OR for presence of 100 or more naevi ≥ 2mm or above in diameter versus 0 - 4 naevi in cases: controls was 7.7 (95% CI 3.8 - 15.8, p < 0.0001). Atypical naevi gave the highest risk for melanoma. AMS Phenotype was strongly predictive of an increased risk of melanoma outside the familial context. The authors concluded that the results favour expression of AMS phenotype as a continuous phenotype, since risk of melanoma increased with increasing AMS score. Melanoma was

associated with naevi on sun exposed and non sun exposed areas. AMS phenotype was more common in males than females (p = 0.008).

- The systematic review and meta-analysis undertaken by Gandini et al. (2005) found the number of common naevi to be an important risk factor for melanoma with a substantially increased risk associated with the presence of 101-120 naevi compared with <15 (RR 6.89; 95% CI 4.63 - 10.25) as was the number of atypical naevi (RR 6.36, 95% CI 3.80 - 10.33; for 5 versus 0).

- A case control study by Osterlind et al. (1988) found major risk factors to be: number of raised naevi on the arms (RR for 5 or more versus none 5.1, 95% CI 3.3-7.9), degree of freckling (RR for many versus none 2.9, 95% CI 2.1-4.1) and light hair colour (RR for blonde/fair versus dark 1.7, 95% CI 1.0-2.9).

- The expert review by Kefford et al. (1999) reported that less than 1-2% of melanoma cases are thought to be attributable to mutations of melanoma susceptibility genes (CKKN2A and CDK4). High familial risks for melanoma included multiple affected family members (RR 35 - 70), previous primary melanoma (RR 8.5), one or more affected first degree relatives (RR 2 - 3), multiple / atypical moles (RR 2 - 12), fair skin (RR 1.4), freckling (RR 2 - 3), blue eyes (RR 1.6), red hair (2.4 - 4) and history of blistering sunburn (RR 2 - 3). Recommended management of genetically predisposed individuals includes education for sun protection and self examination and appropriate dermatological examination commencing from 10 years and when naevi are unstable e.g. puberty, pregnancy. Routine surgical removal of pigmented lesions is not recommended except where melanoma is suspected.

- The retrospective study of familial risk of melanoma by Hemminki, Zhang, and Czene (2003) found the standardised incidence ratio (SIR), for melanoma in offspring to be 2.4 (95% CI 2.1-2.72) when 1 parent has melanoma, 2.98 (95% CI 2.54-3.47) when a sibling is affected and 8.92 (95% CI 4.25-15.31) when both a parent and sibling are affected.

Of the melanoma types superficial spreading melanoma showed the highest familial risk. The authors concluded that there is equal risk of an individual developing melanoma where a sibling or parent are affected and highest risk where two offspring and a parent are affected.

- The expert review by Wachsmuth, Harland, and Bishop (1998) reported that whilst correlation between CDKN2 mutation and presence of atypical naevi phenotype is poor, with variation observed within and between families, ‘carriers' were found to have a greater number of total naevi ($p = 0.003$) and atypical naevi score ($p = 0.02$). The authors concluded that due to poor correlation within families, use of the atypical mole syndrome phenotype to identify candidates for surveillance is inappropriate, and that all members of families with the CDKN2 mutation should be considered as potential carriers with increased risk for melanoma. (ER)

- The case series study by Newton Bishop et al. (1994) reported on clinical characteristics of 13 families with frequent cases of melanoma and AMS in which melanoma onset was significantly younger than in the general population. The AMS score varied across melanoma patients and within families, supporting variability of phenotype expression. There was a high rate of patients with melanoma with > 100 naevi ≥ 2 mm in diameter, and located in unusual regions e.g. ears, buttocks and dorsum of feet. The authors concluded that the study supported the assertion that an autosomal dominant gene may be responsible for melanoma in some families.

**Congenital Melanocytic Naevus syndrome**

**Observational studies which address the risk of melanoma arising from congenital melanocytic naevi (CMN) reach no strong consensus on the threshold sizes of CMN that are important, but in general CMN that are regarded as important are those greater than 20 cm in largest diameter, or covering greater than 5 % of body area.**

**The same level of evidence suggests that children with large CMN are at greatly increased risk of cutaneous and non cutaneous melanoma and there is evidence suggestive of a need for continuous surveillance. Larger CMN pose a greater risk than smaller lesions. Small CMN (< 10 cm) are also precursors to melanoma i.e. predominantly epidermal melanoma which largely occur after puberty. Giant nevi (> 20 cm) pose a risk for dermal melanoma predominantly in pre-pubescent children, although these naevi may also produce epidermal melanomas after puberty.**

**Congenital melanocytic naevi**

- The prospective case series study by Marghoob et al. (1996) investigated the risk of development of melanoma in children born with large congenital melanocytic naevi (LCMN) ≥ 20 cm in largest diameter and found the standardised morbidity ratio for development of melanoma (adjusted RR) to be 239 ($p < 0.001$). The authors concluded that patients with LCMN are at increased risk of cutaneous and non cutaneous melanoma and should be kept under continuous surveillance.

- The retrospective study by Swerdlow, English, and Qiao (1995) investigated the risk of melanoma in patients with congenital naevi, with age ranging from infant - 43 years. Among patients with a congenital naevus covering at least 5% of the body area the relative risk of melanoma mortality was 1046 (95% CI, 127 to 3779) with similar results for naevi 20 cm or more in size. The difference in melanoma mortality risk between the group with a nevus covering at least 5% of the body and the group with smaller nevi was significant ($p < 0.05$). The authors concluded that there is a large risk of melanoma in patients with naevi covering more than 5% of the body surface area. In patients with naevi covering 0 – 4 % of body area no melanomas occurred but the authors suggested that there may also be a sizeable risk of melanoma in this group.

- The retrospective review of histology slides undertaken by Illig et al. (1985) concluded that small CMN (< 10 cm) are precursors to melanoma i.e. predominantly epidermal melanoma which largely occur after puberty. Giant nevi (> 20 cm) pose a risk for dermal melanoma predominantly in pre-pubescent children, whereas these naevi may also produce epidermal melanomas after puberty.

# EVIDENCE TABLE 6.1

## *What are the needs of individuals at increased familial risk of melanoma?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bataille *et al.* 1996) | To investigate which naevus phenotype is the most predictive of melanoma in the general population. | Case-control study using melanoma cases with hospital out patient and community patient controls. Subjects evaluated by clinical examination and interview. Acute mole syndrome (AMS) phenotype defined using a scoring system based upon 5 clinical features. | Study designed to relate to general population (North East Thames region). 426 melanoma patients aged 16-75 compared with 416 controls from same age group.<br><br>**UK** | OR of 4 or more atypical naevi versus one in cases: controls was 28.7 [8.6-95.6], p < 0.0001). OR for 100 or more naevi 2mm or above in diameter versus 0-4 naevi in cases: controls was 7.7 [3.8-15.8] p < 0.0001. | Atypical naevi gave the highest relative risk for melanoma. AMS Phenotype was strongly predictive of an increased risk of melanoma outside the familial context. Results of study favour expression of AMS phenotype as a continuous phenotype, since risk of melanoma increased with increasing AMS score. Melanoma was associated with naevi on sun exposed and non sun exposed areas. AMS phenotype was more common in males than females (p = 0.008). | No individual matching, but approximate frequency matching performed for age and sex. Confidence intervals and p values given throughout. | 2 + |
| (Hemminki *et al.* 2003) | To estimate familial risk in invasive and in situ melanoma. | Retrospective analysis of large cancer database, retrieving melanoma data from 1961 to 1998, verified histologically. 24818 cases of invasive and 5510 cases of in situ melanoma analysed. | People in families (parent, sibling, children) where melanoma has occurred to at least one family member. Age 0-66 years.<br><br>**Sweden** | Standardised incidence ratios (SIR), Populated attributable fraction by proband status., Person-years at risk and 95% CI calculated. | SIR for offspring 2.4 [2.1-2.72] when 1 parent has melanoma, 2.98 [2.54-3.47] when only a sibling is affected and 8.92 [4.25-15.31] when both a parent and sibling are affected. Of the melanoma types superficial spreading melanoma showed the highest familial risk. Author concludes equal risk where a sibling or parent is affected; highest risk where two offspring and a parent are affected. | CI for cases in offspring based upon Poisson distribution. Expected numbers based upon general Swedish population data. European Standard Population used for standardisation. Data adjusted for socio-economic status. Parental age limited to 66 years to make it comparable with offspring population. Appraised with 'Harm/aetiology study' tool by | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | | Badenoch and Heneghan (2002). | |
| (Illig *et al.* 1985) | To investigate the risk of development of melanoma in patients with congenital melanocytic naevi (CMN) less than 10 cm in largest diameter. | Retrospective review of histological slides from a multi-centre case series of 52 patients. | Patients with CMN ranging from < 1.5 cm to > 20 cm in largest diameter.<br><br>**Germany** | Occurrence of CMN associated melanomas, classified by tumour type and by characteristics of precursor CMN i.e. 'superficial' versus 'deep'. | 52 melanoma tumours arose from the CMN lesions: 47 invasive melanomas, 2 in situ melanomas and 3 severe focal melanocytic dysplasias. The age at melanoma diagnosis ranged from 18 to 79 years. No prepubertal melanoma was observed. Authors conclude that small CMN (< 10 cm) are precursors to melanoma, predominantly epidermal and after puberty. Giant nevi (> 20 cm) pose a risk for dermal melanoma predominantly in children, whereas these naevi may also produce epidermal melanomas after puberty. | Definitions used: Largest diameter of CMN > 20 cm 'large', 10 - 20 cm 'medium' and three 'small' subgroups: > 3 cm, 1.5 - 3 cm and < 1.5 cm. 'Congenital' status defined by known histological features. No incidence information provided since numbers of patients with CMN but without melanoma not reported. Role of depth of CMN alluded to, in relation to size of CMN. | 3 - |
| (Gandini S *et al.* 2005) | To estimate the risk of melanoma considering the number of common naevi and the number of atypical naevi as risk factors. | Meta analysis of 46 primary studies with 47 datasets for analysis.<br><br>Case control, cohort and cross sectional studies that provided sufficient data for calculation of RR, 95% CI. | Patients with high numbers of common naevi or with atypical naevi.<br><br>**Undertaken in Italy and France** | RR of histologically confirmed melanoma. | The number of common naevi was confirmed an important risk factor with a substantially increased risk associated with the presence of 101-120 naevi compared with <15 (pooled Relative Risk (RR) = 6.89; 95% Confidential Interval (CI): 4.63, 10.25) as was the number of atypical naevi (RR = 6.36 95%; CI: 3.80, 10.33; for 5 versus 0).<br><br>The type of study and source of cases and controls were two study characteristics that significantly influenced the estimates. Case-control studies, in particular when the hospital was the source for cases or controls, appeared to present much lower and more precise estimates than cohort studies. | Methods thoroughly reported.<br><br>MEDLINE and EMBASE databases searched, with no language restrictions.<br><br>Studies of congenital naevi excluded.<br><br>Measure of study heterogeneity performed. | 1 ++ |
| (Kefford *et al.* 1999) | To provide evidence based guidance on genetic counselling for genetic predisposition to melanoma. | Expert review (52 references) by the Melanoma Genetics Consortium. | Individuals at increased risk of melanoma: largely concerning families, considering genetic testing and also observable traits. Authors note | Recommendations set out. | Less than 1-2% of melanoma cases are thought to be attributable to mutations of melanoma susceptibility genes (CKKN2A and CDK4). 20 - 40 % of families with 3 or more affected (have melanoma) show inheritance of mutations in the CDKN2A gene. Many aspects of genetic mechanisms are not | Consensus of an international consortium of experts. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | applicability to individuals at increased risk in addition.<br><br>**Produced by international consortium** | | fully understood e.g. penetrance. High familial risks for melanoma include multiple affected family members (RR 35 - 70), previous primary melanoma (RR 8.5), one or more affected first degree relatives (RR 2 - 3), multiple / atypical moles (RR 2 - 12), fair skin (RR 1.4), freckling (RR 2 - 3), blue eyes (RR 1.6), red hair (2.4 - 4) and history of blistering sunburn (RR 2 - 3). Genetic testing is not recommended as routine care outside the context of research. Two groups warranting special consideration are families in which a CDKN2A mutation is identified through a research study and families in which no prior testing of affected individuals has been carried out. Careful counselling is required in these instances. Recommended management of genetically predisposed individuals includes education for sun protection and self examination and appropriate dermatological examination commencing from 10 years and when naevi are unstable e.g. puberty, pregnancy. Routine surgical removal of pigmented lesions is not recommended except where melanoma is suspected. | | |
| (Marghoob *et al.* 1996) | To define the risk of development of melanoma in children born with large congenital melanocytic naevi (LCMN). | Prospectively followed up case series study of patients recorded on a registry between 1979 and 1993, matched with controls of same age/sex from the general population. | 92 patients (median age 3 years) with large congenital melanocytic naevi (LCMN) 20 cm or more in largest diameter.<br><br>**US** | Standardised morbidity ratio. | 41% of individuals were males and 59% were females. Mean follow-up was 5.4 years. 61% of cases underwent surgery for the LCMN. NB - there is no consensus on the definition of large congenital melanocytic naevi. melanoma developed in 3 (3.3%) of the 92 patients within an average 23.3 months of follow-up (anatomical location: 2 x central nervous system and 1 x retroperitoneum). All 3 of these cases had satellite lesions. Standardised morbidity ratio (adjusted RR) estimated as 239 ($p < 0.001$). | Reviewer's comments: Role of controls uncertain i.e. were they actively recruited into the study? Value of including predicted size of lesion in adulthood unknown. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Authors conclude that patients with LCMN are at increased risk of cutaneous and non cutaneous melanoma and should be kept under continuous surveillance. | | |
| (Newton Bishop *et al.* 1994) | To report on clinical characteristics of 13 families with frequent cases of melanoma and AMS, and to evaluate use of a scoring system to define AMS. | Case series of 13 families. | 13 families selected (from over 100 families recruited) on the basis of numerous cases of melanoma and AMS phenotype and inheritance suggestive of autosomal dominant pattern (inherited susceptibility). Physical examination of families undertaken and pedigrees established.<br><br>**UK** | Association between AMS score amongst families and characteristics of patients with melanoma and their family members. | 60 melanomas were seen in 37 individuals. Of 34 patients for whom details were reliable, mean age was 42.3 years versus 51.7 years, known from the general population ($p < 0.001$). 57% of 21 living patients with melanoma scored 3 or more on the AMS scale, as did 38% of first degree relatives and 26% of distant relatives. This was not statistically significant but tentatively suggestive of genetic predisposition of melanoma and AMS. AMS score did not correlate with age of onset of melanoma ($p > 0.3$) but there was strong correlation between AMS score and multiple melanoma in the same individuals ($p = 0.01$). The AMS score varied across melanoma patients and within families, supporting variability of phenotype expression. Several families had melanoma cases without AMS. 41% of families for whom clear clinical evidence of AMS was available scored 3 or more on the AMS scale. There was a high rate of patients with melanoma with > 100 naevi 2 mm or more in diameter, and located in unusual regions e.g. ears, buttocks and dorsum of feet. Authors conclude that the study supports the assertion that an autosomal dominant gene may be responsible for melanoma in some families. | Authors note that in a London hospital patients with melanoma commonly have > 100 naevi 2 mm or more in diameter, and located in unusual regions e.g. ears, buttocks, scalp, iris and dorsum of feet. AMS scoring system is based upon no. naevi, degree of clinical atypia, abnormal distribution and pigmented lesions of the iris. Scale is 0 - 5, handled dichotomously in this study i.e. 0 - 2 (no AMS) vs. 3 - 5 (AMS affected). | 3 - |
| (Osterlind *et al.* 1988) | To explore the relationship between melanoma and host factors: hair, eye and skin colour; raised naevi | Case-control study using histologically confirmed melanoma cases versus population | Study designed to be generalisable to the general population in Denmark. 474 | Risk ratios calculated (not OR) for host factors with many estimates mutually adjusted | Major risk factors were found to be: number of raised naevi on the arms (RR 5.1 [3.3-7.9] for 5 or more versus none), degree of freckling (RR 2.9 [2.1-4.1] for many versus none) and light hair colour | Interviewers blind to case/control status and also hypothesis under study. RR used in this Case-control study, not OR. | 2 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | on the arms, naevi size; tanning ability and freckling. | controls, with host factors collected by interview by a reviewer blind to case/control status. | melanoma cases compared with 926 population controls selected at random from the census. Lentigo maligna melanoma cases excluded from study.<br><br>**Denmark** | and adjusted for sex. | (RR 1.7 [1.0-2.9] for blonde/fair versus dark). | | |
| (Swerdlow *et al.* 1995) | To analyze cause specific mortality and cancer incidence risks in patients with congenital naevi according to the size of the nevi. | Retrospective study of a case series treated at a single hospital from 1950 to 1984 for mortality to mid 1993 and for cancer incidence from 1971 to 1989. | 265 patients with congenital naevi (age infant - 43 years) who had been treated at a children's' hospital including 33 patients with large naevi (i.e. > 5% of total body area).<br><br>**UK** | Mortality and cancer incidence rates compared with expectations from national mortality / incidence rates by age and sex. | Among the 33 patients with a congenital naevus covering at least 5% of the body area, two melanomas occurred during follow-up; both were fatal. The relative risk of melanoma mortality in these patients was 1046 (95% CI, 127 to 3779) with similar results for naevi 20cm or more in size. Both melanoma cases were individuals aged over 15 years. In the remaining 232 patients, 68 of whom had a naevus covering 1% to 4% of the body, and 164 with nevi smaller than 1% of body area, no melanomas occurred (0.18 melanoma deaths expected). The difference in melanoma mortality risk between the group with a nevus covering at least 5% of the body and the group with smaller nevi was significant ($p < 0.05$). There was no significantly increased risk of nonmelanoma mortality or of nonmelanoma cancer incidence overall, although two lymphohematopoietic malignancies occurred. The authors conclude that there is a large risk of melanoma in patients with naevi covering more than 5% of the body surface area. The results do not support the hypothesis of greatly increased risk in persons with congenital nevi smaller than this, but because the confidence intervals of the result were wide, the data are compatible with a sizable risk. | | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Wachsmuth *et al.* 1998) | To report on the atypical mole phenotype, familial risk of melanoma and association with CDKN2 genetic mutation in the context of melanoma risk. | Letter to journal editor citing previous studies (expert review). | Families with atypical mole syndrome and/or CDKN2 gene mutation.<br><br>**UK** | Correlation of CDKN2 mutation, with no. of atypical naevi observed and also with atypical naevi score and total no. of naevi observed. | Correlation between CDKN2 mutation and presence of atypical naevi phenotype was poor, with variation within and between families. 'Carriers' had greater number of total naevi (p = 0.003) and atypical naevi score (p = 0.02) after adjustment for differences between families. No significant difference was found for absolute no. of atypical naevi. Authors conclude that due to poor correlation within families, use of the atypical mole syndrome phenotype to identify candidates for surveillance is inappropriate, and that all members of families with the CDKN2 mutation should be considered as potential carriers with increased risk for melanoma. | Atypical mole syndrome phenotype considered present/absent for individuals using a tool (details not included). | 4 + |

# Lymphoma

### The questions

*What are the needs of patients with cutaneous lymphoma?*

### The nature of the evidence

Six studies were identified as follows:

- One RCT, of good quality
- Two observational studies, one of good quality and one of poor quality
- One set of clinical guidelines of good quality
- Two expert reviews of good quality.

One observational study is reported in two papers. Two studies are from the UK, two are from the US and one study each is from France and Switzerland. Generalisability to the UK is reasonable, but limited.

### Summary of the supporting evidence for the recommendations

**Evidence from an expert review suggests that quality of life of patients with cutaneous lymphoma may be severely affected over many years. Five year survival varies according to lymphoma type and is estimated to be 70–90% in patients with mycosis fungoides and 10–50% in patients with Sézary syndrome.**

**RCTs have shown that early intervention in mycosis fungoides using multi-agent chemotherapy does not improve survival but does increase morbidity and clinical guideline evidence supports avoidance of toxic or aggressive therapies in the treatment of patients with early stage disease. Skin directed treatment (topical therapy, superficial radiotherapy and phototherapy) has been shown to achieve long periods of remission and is the most appropriate therapy in early stage disease.**

**Evidence from one observational study and one expert review supports the role of total skin electron beam therapy (TSEB) to treat patients with mycosis fungoides, with an overall response rate reported as 94.7% and disease free survival at five years estimated at 50%. Megavoltage radiotherapy can be used to palliate extracutaneous disease.**

**Evidence from one small, prospective, non randomised therapeutic trial suggests that autologous, peripheral blood stem cell transplantation can bring about remission, but not cure, of mycosis fungoides; most patients showed disease control at the time of relapse by conventional therapy.**

**Clinical guideline and expert review evidence is supportive of multidisciplinary management of patients with cutaneous lymphoma by health professionals with the appropriate expertise.**

- The expert review by Dummer, Hess-Schmid, and Burg (2000) stated that whilst cutaneous lymphoma is confined to the skin for many years, quality of life in patients with cutaneous lymphoma can be severely affected. CTCL constitutes 65% of all cutaneous lymphomas and usually has good prognosis: Patients with mycosis fungoides have 5 year survival of 70-90%. Patients with CD30+ lymphoma have 5 year survival of 90%. CD30- lymphomas have poorer prognosis. 5 year survival for Sezary Syndrome is 10-50%. Standard cytotoxic therapy has limited efficacy due to slow proliferation and the possibility of complete remission is debated. Corticosteroids, retinoids and UV therapy can achieve long lasting remissions.

- The RCT comparing combination radiotherapy / chemotherapy versus conservative topical treatment in patients with mycosis fungoides undertaken by Kaye et al. (1989) found that the combined therapy produced considerable toxicity and that although patients receiving combined therapy had a significantly higher rate of complete response than patients receiving conservative therapy, there was no significant

difference between the treatment groups in disease-free or overall survival.

- The small case series study of patients with tumour stage mycosis fungoides reported by Olavarria et al. (2001) and Russell-Jones et al. (2001) found that autologous, peripheral blood stem cell transplantation (PBSCT) brought about complete remission with median duration of 7 months (range 2-14 months). The median survival post transplant was 11 months (range 0-41 months) and the authors concluded that PBSCT can bring about remission, but not cure, of mycosis fungoides and that despite the short interval to relapse, most patients achieved good disease control at the time of relapse by conventional therapy.

- The clinical guidelines produced by Whittaker et al. (2003) recommend that all patients should be reviewed by a MDT comprising dermatologist, clinical / medical (haemato) oncologist, dermatopathologist, with support from an immunophenotypic laboratory. Skin directed treatment (topical therapy, superficial radiotherapy and phototherapy) is the most appropriate therapy in early stage disease, where toxic / aggressive therapies should be avoided. In later disease stages, total skin electron beam radiation (TSEB) and superficial radiotherapy are effective treatments.

- The retrospective case series study of patients with mycosis fungoides undertaken by Ysebaert et al. (2004) found that at three months after TSEB, the overall response rate was 94.7%. A complete response was achieved in 87.5% of patients with disease affecting < 10% of skin and 84.8% in patients with disease affecting >10% of skin. 5-year disease free survival was 50%. Overall survival at 5/10/15 years was 90%/65%/42%, respectively. The authors concluded that TSEB is highly effective in early-stage mycosis fungoides without adjuvant therapy.

- The expert review by Hoppe (2003) stated that radiotherapy is the most effective single agent for the treatment of mycosis fungoides, with total

skin electron beam therapy (TSEB) as an important form of management, especially for patients who have widespread disease. Megavoltage radiotherapy may also be used selectively for palliative treatment of extracutaneous disease.

# EVIDENCE TABLE 6.2

## *What are the needs of patients with cutaneous lymphoma?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Dummer *et al.* 2000) | To provide an overview of the Cutaneous T Cell Lymphomas and aspects of epidemiology, treatment and quality of life. | Expert review i.e. unsystematic literature review (30 references). | Patients with cutaneous lymphoma.<br><br>**Switzerland** | Salient points from primary studies of prognosis, treatment and quality of life. | • Key points: Defined as lymphoproliferative disorders manifesting in the skin and confined to the skin for many years.<br>• Incidence estimated as 2 per million in the US / Scandinavia.<br>• Association with HTLV-1 is reported in the literature, however molecular studies suggest a minor role in a small proportion of patients with the disease.<br>• CTCL constitutes 65% of all cutaneous lymphomas and usually has good prognosis: Patients with MF have 5 year survival of 70-90%. Patients with CD30+ lymphoma have 5 year survival of 90%. CD30- lymphomas have poorer prognosis. 5 year survival for Sezary Syndrome is 10-50%.<br>• Quality of life can be severely affected in CTCL. Physical symptoms include pain, pruritus and sleep deprivation, and can last many years. Many people with CTCL deliberately avoid beaches and swimming pools, and the impact upon quality of life has been | All findings cited from primary studies. | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | quantified as similar to that of colon or lung cancer.<br>• Standard cytotoxic therapy has limited efficacy due to slow proliferation and the possibility of complete remission is debated. Corticosteroids, retinoids and UV therapy can achieve long lasting remissions.<br><br>Author concludes:<br>• Provision of precise information to patients on the nature of CTCL is a substantial support. | | |
| (Hoppe 2003) | To review the role of radiotherapy in the treatment of mycosis fungoides. | Expert review (49 references). | Patients with mycosis fungoides.<br><br>**US** | Outcomes on efficacy and development of techniques in radiotherapy, based upon primary studies. | Radiotherapy is the most effective single agent for the treatment of mycosis fungoides.<br><br>There are well-defined dose-response relationships for achieving a complete response as well as the durability of this response. Complete responses generally require doses of 7 Gy or higher and for total skin electron beam therapy (TSEB), 94% response rates can be achieved for doses of 30 Gy or higher.<br><br>Techniques of electron beam therapy have been developed that permit treatment of the entire skin.<br><br>TSEB is an important form of management, especially for patients who have thick generalized plaque or tumourous disease, although the palliative role is generally more accepted than the disputed curative role. Following TSEB, 25% of patients with extensive plaques can be disease free at 5 years.<br><br>Megavoltage radiotherapy may also be | | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | used selectively for palliative treatment of extracutaneous disease. | | |
| (Kaye *et al.* 1989) | To determine whether aggressive radiotherapy and chemotherapy therapy is the optimal initial therapy for patients with cutaneous lymphoma, compared to conservative therapy. | RCT comparing combination therapy of 3000 cGy electron beam radiotherapy plus multi agent chemotherapy versus conservative treatment consisting of sequential topical treatment. | 103 patients with mycosis fungoides of any disease stage: 52 patients in combination therapy group and 51 in the topical treatment group.<br><br>**US** | Response rate.<br><br>Disease free survival.<br><br>Overall survival. | **Side effects**<br>Combined therapy produced considerable toxicity: 12 patients required hospitalization for fever and transient neutropenia, 5 had congestive heart failure, and 2 were later found to have acute nonlymphocytic leukaemia.<br><br>**Rate of response**<br>Patients receiving combined therapy had a significantly higher rate of complete response, documented by biopsy, than patients receiving conservative therapy (38 percent vs. 18 percent; P = 0.032). After a median follow-up of 75 months, however, there was no significant difference between the treatment groups in disease-free or overall survival.<br><br>Authors conclude that early aggressive therapy with radiation and chemotherapy does not improve the prognosis for patients with mycosis fungoides as compared with conservative treatment beginning with sequential topical therapies. | Patients with high co morbidity (unrelated to mycosis fungoides), or previously treated with systemic chemotherapy or total skin electron beam therapy were ineligible for the study.<br><br>Patients were stratified according to presence / absence of visceral disease and whether previous topical treatment had been received.<br><br>Study protocol included that in the conservative therapy group, radiotherapy commenced when disease became progressive and poorly controlled.<br><br>2 patients refused treatment after randomisation to combination therapy and were lost to follow-up.<br><br>Patients' demographic and disease characteristics were similar between groups.<br><br>Trial size based upon power calculation.<br><br>Analysis is by intention to treat.<br><br>Neither patients nor investigators were blinded to randomised therapy. | 1 + |
| (Olavarria *et al.* 2001) | To report on the outcomes of nine | Small case series of patients treated | 9 patients with tumour stage | Disease-free survival and overall | Eight patients engrafted promptly and one patient died of septicaemia. All | Karnofsky score > 90% in all patients at the time of | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | patients who received autologous stem cell transplants as therapy for mycosis fungoides. | at a single centre. | mycosis fungoides, resistant to conventional therapy, median age 47 years (range 27-67 years), median duration of disease prior to study entry 61 months (range 4-340 months).<br><br>**UK** | survival. | survivors entered complete remission.<br><br>Seven patients have relapsed at a median of 7 months (2-14) post stem cell transplant. However, most patients have relapsed into a less aggressive stage, which has responded to conventional therapy.<br><br>The median duration of complete remission was 7 months (range 2-14 months). The median survival post transplant was 11 months (range 0-41 months) with an estimated actuarial probability of survival of 53 % at 3 years.<br><br>Authors conclude that autologous stem cell transplant is feasible, safe and can result in complete remission in a significant proportion of patients with tumour stage mycosis fungoides. Despite a short relapse-free survival, most patients achieved good disease control at the time of relapse. | transplantation.<br><br>Patients had received various initial therapies, often PUVA and local, superficial radiotherapy.<br><br>Median follow-up 29 months (range 11-43 months).<br><br>NB same trial as that by Russell-Jones et al. (2001): see below. | |
| (Russell-Jones *et al.* 2001) | To establish which factors affect disease free survival and whether peripheral blood stem cell transplantation (PBSCT) improves overall survival. | Small, prospective case series with PBSCT as intervention. | 9 patients with tumour stage mucosis fungoides who had failed conventional therapy (median duration of disease since diagnosis 9 years, median duration of tumour stage disease 2.8 years).<br><br>**UK** | Disease free survival and overall survival. | 1 patient failed to engraft and subsequently died. The other 8 patients entered a period of complete remission: in 4 patients this was short lived with median 2 months. Median overall survival was 9.5 months in this group.<br><br>3 other patients relapsed after median 11 months and 1 patient remains disease free at 5 months follow-up. The median overall survival was 23.5 months in this group.<br><br>Stage at transplant did not predict outcome.<br><br>Disease duration: tumours started 2.5 years prior to transplant in rapid relapse | Patients under 70 selected with no co morbidity. No statistical significance found (n = 9). Patients differed in their previous therapies and conditioning therapies.<br><br>NB same trial as that by Olavarria et al. (2001): see above. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | group. Differences in conditioning regimens did not predict relapse. Persistence of T cell clone in the graft or failure of the conditioning regimen to achieve disease clearance, or both. Presence of T cell clone in peripheral blood appeared to influence survival.<br><br>Authors conclude that PBSCT can bring about remission but not cure of mycosis fungoides. Transplant of neoplastic cells may be avoidable by harvesting at an earlier stage in the disease process. | | |
| (Whittaker *et al.* 2003) | To provide recommendations for the initial assessment, histological investigation and therapy of cutaneous lymphoma. | Evidence based clinical guideline. | Patients with cutaneous lymphoma.<br><br>**UK** | Recommendations for practice. | **Epidemiology**<br>Incidence of cutaneous lymphoma is 0.4 per 100 000 per year but due to long term survival in most patients, prevalence is higher.<br><br>Two thirds of cutaneous lymphoma are cutaneous T cell lymphomas (CTCL), the majority of which are mycosis fungoides. The disease is commoner in males.<br><br>**Organisation of services**<br>Authors recommend that all patients are reviewed by a MDT comprising dermatologist, clinical / medical (haemato) oncologist, dermatopathologist, with support from an immunophenotypic laboratory.<br><br>**Treatments**<br>Skin directed treatment (topical therapy, superficial radiotherapy and phototherapy) is the most appropriate therapy in early stage disease.<br><br>Most cases of early stage mycosis fungoides are multifocal, with recurrent disease throughout life and normal life expectancy, warranting avoidance of | Evidence based clinical guideline - concerned with clinical issues. 26 specific clinical recommendations not summarised here. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | toxic/aggressive therapies.<br><br>Late stage mycosis fungoides has poorer prognosis and there is lack of consensus on the best treatment. CTCL is very radiosensitive and total skin electron beam radiation (TSEB) and superficial radiotherapy are effective treatments.<br><br>Overall response rate to various treatments is estimated as 30% and complete response as 10%.<br><br>Chemotherapy produces a high response rate (30 %) but this effect is short lived (median duration 3 - 41 months).<br><br>This suggests that no therapy so far has improved outcome to any great effect and that only patients with responsive disease benefit. Patients with late stage disease should be entered onto clinical trials.<br><br>Patients' quality of life and realistic expectations must be considered when considering therapy. Palliative care should be considered for patients with late stage disease or poor performance status. | | |
| (Ysebaert *et al.* 2004) | To report on the experience of a single institution in the treatment of T1 and T2 mycosis fungoides (MF) with total skin electron beam therapy (TSEB). | Retrospective case series. | 141 patients with histologically proven mycosis fungoides were referred to the radiotherapy department for treatment by TSEB.<br><br>Mean total dose was 30 Gy, 2 Gy/day, 4 days/week, for 4 | Response measured at three months after TSEB.<br><br>Relapse-free rate, overall survival rate, and management of recurrence.<br><br>Outcomes reported | Three months after completion of TSEB, the overall response rate was 94.7%. A complete response was achieved in 87.5% of T1 and 84.8% of T2 patients.<br><br>31 patients (54.4%) experienced a skin failure (8 with T1 and 23 with T2 disease) within 1 year. 18/ 31 patients received further TSEB as salvage.<br><br>After a second course of TSEB (4 T1 | Prior to TSEB 43.8% of patients had received steroids, chemotherapy, retinoids or interferon, but no patients had received prior radiotherapy.<br><br>Some patients also received adjuvant or salvage therapy.<br><br>Kaplan Meier methods used | 3 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | weeks.<br><br>Median age was 61 years (range, 19-84).<br><br>**France** | by proportion of involved skin:<br><br>T1: < 10%<br>T2: >10%. | and 10 T2 patients), the 5-year freedom from relapse rate was 70% vs. 39% in patients having received other treatments.<br><br>For the whole group, 5-year disease free survival was 50%. The 5/10/15-year overall survival were 90%/65%/42%, respectively.<br><br>In univariate analysis, T1 ($p = 0.03$), complete response after first TSEB ($p = 0.04$), and age younger than 60 ($p < 0.001$) were significant prognostic factors for overall survival.<br><br>In multivariate analysis, age younger than 60 years was statistically associated with improved overall survival ($p = 0.001$) whereas T stage and complete response were not significant ($p = 0.059$ and $p = 0.063$, respectively).<br><br>During the mean 86-month period of follow-up from relapse, a second recurrence was observed in 29% of patients.<br><br>Authors conclude that TSEB is highly effective in early-stage MF without adjuvant therapy. Management of relapses with local radiotherapy or second TSEB is feasible, time-saving, and cost effective. | for survival analysis.<br><br>Median follow-up was 114 months (range, 14-300). | |

# Kaposi's sarcoma

### The questions

*What are the effective treatments for patients with AIDS related Kaposi's sarcoma (KS)?*

### The nature of the evidence

Five studies were identified as follows:

- Two observational studies, one of good quality and one of fair quality
- Three expert reviews of good quality

Two studies are from the UK, two are from Italy and one study is from France. Generalisability to the UK is reasonable. All of the studies address people with AIDS related KS.

### Summary of the supporting evidence for the recommendations

**Expert review evidence supports highly active anti retrovirus therapy (HAART) as an effective treatment for KS, which is associated with a dramatic decrease in incidence of lesions and which can bring about tumour regression. Observational study evidence suggests that HAART is associated with prolonged disease control in patients with KS.**

**Evidence from one observational study suggests that radiotherapy is also an effective treatment for AIDS related KS, with a high response rate reported. Expert review evidence reports that local therapies, including radiotherapy and topical drug treatments, are effective for treating patients with early skin lesions and that in general, systemic chemotherapy for KS is a treatment option for patients with widespread, symptomatic disease.**

- The retrospective case series study by Bower et al. (1999) found the median time to treatment failure for patients with KS treated with

HAART was 1.7 years, compared with 0.5 years for the same sample of patients before they started HAART therapy.

- The expert review by Cattelan, Trevenzoli, and Aversa (2002) stated that HAART is an essential approach in the management of KS in most, if not all, patients with AIDS-related KS and that in general, systemic treatment for KS is limited to widespread, symptomatic disease, whereas local interventions are indicated for minimal, cosmetically troublesome lesions.

- The case series study by Kirova et al. (1998) found that 92% of 6464 irradiated cutaneous fields (from a total of 643 patients with AIDS related KS in the study, where a proportion of fields were of mucosal skin) showed a partial or complete response to radiotherapy.

- The expert review by Lukawska, Cottrill, and Bower (2003) noted that although the incidence of malignancies in HIV positive people has reduced, the rate of HIV infection has continued to rise, whereas the use of HAART has led to a decline in the incidence of KS.

- The expert review by Toschi et al. (2002) reported that response rates of between 27% and 92% can be achieved through the use of intralesional or topical cytotoxic chemotherapy, depending on the agent used. Systemic therapy with cytotoxic chemotherapy is warranted for widely disseminated, progressive or symptomatic disease. KS lesions are highly radiosensitive and response rates greater than 80% are well documented.

# EVIDENCE TABLE 6.3

## *What are the effective treatments for patients with AIDS related KS?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Bower *et al.* 1999) | To evaluate the impact of highly active antiretroviral therapy (HAART) on KS, by measuring the interval between treatments both before and after starting a HAART regimen. | Retrospective case series study (case note review). | 78 patients who had received systemic or local treatment for AIDS-related KS who subsequently commenced HAART.<br><br>Only 38% of the 78 patients had good risk KS (stage T0I0) at presentation.<br><br>**UK** | Time to treatment failure, defined as:<br><br>Prior to HAART therapy - the interval between the end of the previous therapy for KS and the start of the next new treatment.<br><br>Following the start of HAART – from the date of starting HAART to the first day of treatment for KS. | The median time to treatment failure before starting HAART was 0.5 years.<br><br>Anti-KS treatment was required for 24 (31%) patients.<br><br>The median time to treatment failure for KS from the start of HAART is 1.7 years. This is statistically longer than the time to treatment failure for the same cohort of patients before they started HAART (log rank chi2 = 16.5, p < 0.0001).<br><br>The serum HIV RNA viral load (VL) at the time of KS progression revealed virological failure of HAART (defined as VL > 5000 copies/ml) in 14 of 24 (58%) and good control (VL < 200 copies/ml) in 5 of 24 (21%).<br><br>Authors conclude that HAART is associated with prolonged time to treatment failure in KS. Progression of KS while on HAART is not necessarily associated with virological failure as determined by rising viral RNA titre. | Of 101 patients initially identified from the database, 33 patients were excluded because they commenced new therapy at the same time as HAART.<br><br>Time to treatment failure was plotted using Kaplan Meier method, with log rank test for assessment of significance of differences.<br><br>Prior to commencing HAART, 87% of patients had previously received topical treatment for their KS and 13 % systemic treatment.<br><br>Different types of HAART regimen were used.<br><br>The median follow-up after starting HAART was 12 months (range, 0.5-52 months). | 3 + |
| (Cattelan *et al.* 2002) | To review recently identified treatment | Expert review. | People with AIDS related KS. | Overview of findings of | **Key points:** | Unsystematic review (127 references) | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | options for AIDS related KS. | | **Italy** | preliminary studies. | HAART is an essential approach in the management of most, if not all, patients with AIDS-related KS.<br><br>In cases of aggressive, visceral and/or life-threatening KS, more complex therapeutic schedules have to be taken into account, including chemotherapy, radiotherapy and/or immunotherapy.<br><br>In general, systemic treatment for KS is limited to widespread, symptomatic disease, whereas local interventions are indicated for minimal, cosmetically troublesome lesions. | | |
| (Kirova *et al.* 1998) | To report on the 10 years experience at a single centre on the treatment of AIDS related KS. | Case series. | 643 patients with AIDS related epidemic KS treated with radiotherapy:<br><br>640 men and 3 women with average age 38.5 years (range 20-68 years).<br><br>**France** | Response rate. | In total, 6777 fields were irradiated, as follows: face 1342 (19.8%), eyelid and conjunctiva 362 (5.3%), trunk 1903 (28.1%), upper and lower limbs 2866 (42.3%), genitals 189 (2.8%). and oral cavity 115 fields (1.7%).<br><br>Objective response was observed in 92% (5947/6464) of all cases, treated for cutaneous KS.<br><br>All patients with irradiated oral lesions had an objective response. The overall tolerance was acceptable for the cutaneous lesions.<br><br>By contrast, mucosal reactions were often observed in oral lesions after relatively low doses of radiotherapy.<br><br>Authors conclude that doses of 15 Gy for oral lesions, 20 Gy for lesions involving eyelids, conjunctiva, and genitals, are sufficient to produce shrinkage of the tumour and good palliation of the symptoms. For the cutaneous KS, authors propose 30 Gy given in a local field, using a | 387 patients (60.1 %) had received previous treatment for their KS.<br><br>Radiotherapy consisted of 4 MV or 45-70 kV X-rays, depending on tumour size and location. Doses ranged from 10 to 30 Gy, according to tumour response and toxicity.<br><br>Mean follow-up was 8.2 months (range 2-36 months).<br><br>621 patients were evaluable, 22 of which were either lost to follow-up or died within 1 month of treatment. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | fractionated scheme with small size applicators.<br><br>Radiotherapy has its own place in the management of KS, as an efficient treatment. | | |
| (Lukawska *et al.* 2003) | To review the current literature on the role of radiotherapy in AIDS-related malignancies published since 1997, and report on the experience from two London treatment centres. | Expert review. | People with AIDS related KS.<br><br>**UK** | Overview of findings of preliminary studies. | **Authors report:**<br><br>Although the incidence of malignancies in HIV positive people has reduced, the rate of HIV infection continues to rise.<br><br>The use of HAART has led to a decline in the incidence of KS (KS).<br><br>HAART suppresses viral replication, reduces opportunistic infections and AIDS defining illnesses and mortality in the population of people with HIV.<br><br>HAART has reduced the requirement for radiotherapy in patients with KS and many patients may tolerate chemotherapy due to their improved immunological status.<br><br>Systemic chemotherapy remains a treatment for advanced disease. | 86 references included. Search strategy described in brief. | 4 + |
| (Toschi *et al.* 2002) | To review treatment options for KS. | Expert review. | Relate to populations of Eastern Mediterranean (classical KS), transplant patients and people with HIV AIDS.<br><br>**Italy** | Overview of findings of preliminary studies. | **Authors report:**<br><br>Intralesional cytotoxic chemotherapy can produce complete or partial response rates of between 27% and 92% depending on the agent used.<br><br>KS lesions are highly radiosensitive and response rates greater than 80% are well documented.<br><br>Systemic therapy with cytotoxic chemotherapy is warranted for widely disseminated, progressive or symptomatic disease. The most active | Non systematic review (111 references). | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | drugs include vinca alkaloids, bleomycin, etoposide, liposomal anthracyclines and paclitaxel.<br><br>Pathogenesis based therapies are also available which work by suppressing the formation of KS spindle cells. | | |

# Gorlin's syndrome

### The question

*What are the effective treatments for patients with BCC arising from Gorlin's syndrome?*

### The nature of the evidence

Five studies were identified as follows:

- Three observational studies of poor quality
- Two expert reviews of good quality

One study is from the UK and one study is from Italy. Three studies are from the US and applicability to the UK is limited. All of the studies address treatment of BCC in patients with Gorlin's syndrome.

### Summary of the supporting evidence for the recommendations

**Expert reviews report that people with Gorlin's syndrome have an increased risk of developing BCCs, with onset as early as at age 2 years but usually from puberty to 35 years of age. This risk increases with exposure to sunlight. Patients with the syndrome may develop thousands of BCCs, ranging in size from 1 mm to 10 mm in diameter and most often involving the face, back and chest.**

**Effective treatments reported in expert reviews include curettage / electrodessication, cryosurgery, and for recurrent and aggressive BCC, $CO_2$ laser and Mohs micrographic surgery. Radiotherapy is contraindicated due to the risk of tumour recurrence or enlargement. Other treatments include photodynamic therapy and topical agents including fluorouracil, imiquimod and delta-aminolaevulinic acid.**

**Evidence from case reports or small case series studies suggests that imiquimod is an effective topical therapy for patients with BCC, with no recurrence of BCC reported within up to 8 months follow-up. The same**

**level of evidence supports $CO_2$ laser therapy as a treatment strategy for multiple BCC tumours that are difficult to treat by other surgical techniques, including multiple facial tumours.**

- The small case series study by Micali et al. (2003) found a high level of BCC tumour response in 4 patients with Gorlin's syndrome following topical imiquimod therapy, with no patient suffering a relapse at follow-up with range 4 months to 8 months.

- The expert review by Gorlin (1995) recommended that patients with Gorlin's syndrome should have regular 2-3 monthly visits to a dermatologist, especially during adolescence. Gorlin (1995) cited topical tretinoin and fluorouracil as effective treatments for BCC, and cautiously, oral retinoids since whilst they may control BCCs, toxicity is a risk. Photo dynamic therapy was reported as an emerging treatment.

- The expert review by Manfredi et al. (2004) stated that sunlight is a strong risk factor for BCC in patients with Gorlin's syndrome, with onset of BCC occurring commonly between puberty and 35 years of age, mostly affecting thoracic and cervico-facial areas. Effective treatments include curettage / electrodessication, cryosurgery, and for recurrent and aggressive BCC, $CO_2$ laser and Mohs micrographic surgery. Radiotherapy is contraindicated due to the risk of tumour recurrence or enlargement. Other treatments include PDT and topical fluorouracil, and delta-aminolaevulinic acid.

- The small case series study by Nouri et al. (2002) found that in patients with Gorlin's syndrome, $CO_2$ laser therapy can treat multiple BCCs in a short period of time with minimal scarring and no recurrence at 18 month follow-up.

- The case report of a single patient with multiple facial BCCs arising from Gorlin's syndrome by Doctoroff, Oberlender, and Purcell (2003) found that treatment with $CO_2$ laser therapy was effective.

# EVIDENCE TABLE 6.4

***What are the effective treatments for patients with BCC arising from Gorlin's syndrome?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Doctoroff *et al.* 2003) | To report on the use of $CO_2$ laser to treat BCC. | Case report : single patient. | 1 patient with multiple facial BCC arising from Gorlin's syndrome.<br><br>Age: 32 years.<br><br>**US** | Tumour response. | The patient had received previous extensive Mohs micrographic surgery to facial sites e.g. lip requiring grafting, which failed to completely excise BCC tumours. Previous topical imiquimod had also been applied.<br><br>45 BCC tumours were treated with $CO_2$ laser.<br><br>At 2 months follow-up 2 BCC tumours on the face were treated with Mohs micrographic surgery. 6 BCCs on the back were treated with electrodessication and curettage.<br><br>At 10 month follow-up 4 additional, facial BCCs were identified and treated with Mohs micrographic surgery; which was notably easier than prior to $CO_2$ laser therapy.<br><br>Authors conclude that the management of multiple, facial BCCs in patients with Gorlin's syndrome presents a major challenge and that numerous surgical procedures lead to disfigurement and that $CO_2$ laser therapy is a useful treatment. | Authors were unable to determine whether post treatment BCCs were recurrent or metachronous. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Gorlin 1995) | To describe the clinical features and treatment strategies for nevoid basal cell carcinoma syndrome (NBCCS). | Expert review. | Patients with NBCCS.<br><br>**Undertaken in the US** | Study reports on clinical features and management of NBCCS. | Author states:<br><br>Patients with NBCCS should have regular 2-3 monthly visits to a dermatologist especially during adolescence.<br><br>Presymptomatic genetic diagnosis is a possibility.<br><br>Multicentric, superficial BCCs without follicular involvement can be managed by topical tretinoin and fluorouracil.<br><br>The use of oral retinoids is debated, since whilst it may control BCCs, toxicity is a risk. Furthermore oral etretinate is generally contraindicated in women of child bearing potential.<br><br>Photo dynamic therapy is reported as an emerging treatment. | 151 references. | 4 + |
| (Manfredi *et al.* 2004) | To review the literature on nevoid basal cell carcinoma syndrome (NBCCS). | Expert review. | Patients with NBCCS.<br><br>**Undertaken in the UK** | Study reports on clinical features and management of NBCCS. | Prevalence of NBCCS is generally understood to be around 1 in 60,000.<br><br>Principal clinical features are multiple odontogenic keratocysts, basal cell naevi and skeletal abnormalities.<br><br>The most common skin lesions are BCC tumours, with sunlight as a strong risk factor. Onset occurs between puberty and 35 years of age, and BCCS mostly affect thoracic and cervico-facial areas. Histologically BCCS associated with the syndrome cannot be differentiated from BCCs in general.<br><br>Treatment of BCCs in NBCCS can be difficult owing to the large number of lesions which may occur. | 87 references. | 4 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | Curettage/electrodessication is probably the most effective technique for small, well defined, primary lesions without aggressive histology.<br><br>Cryosurgery may be useful, but is less effective for recurrent BCC.<br><br>Recurrent and aggressive BCC can be treated by $CO_2$ laser, microscopically directed surgery and Mohs micrographic surgery. Radiotherapy is contraindicated due to the risk of tumour recurrence or enlargement.<br><br>PDT and topical delta-aminolaevulinic acid has been suggested only for superficial, flat lesions. Topical fluorouracil may be indicated for low risk, superficial BCC with no hair follicle involvement.<br><br>Children of patients with NBCCS should be investigated for evidence of NBCCS. Genetic examination should be undertaken in the neonatal period. 6 monthly MRI scans until the age of 7 are suggested to detect medulloblastoma.<br><br>Genetic testing is possible in families with a history of NBCCS. | | |
| (Micali *et al.* 2003) | To discuss the role of topical 5% imiquimod cream to treat BCC based upon a small series of patients. | Small case series study. | 4 patients with Gorlin's syndrome, with superficial and nodular multiple BCCs on the face and/or trunk.<br><br>Age range 19 – 70 years.<br><br>**Italy** | Tumour response and recurrence. | Author notes that treatment of BCC includes surgical excision, curettage and electrodessication, cryosurgery, Mohs micrographic surgery and $CO_2$ laser treatment in addition to imiquimod.<br><br>Side effects included erythema, erosion, bleeding and itching. All four patients were able to complete their treatment.<br><br>There was a high level of tumour | Resolution of BCCS was confirmed surgically and histologically.<br><br>Follow-up had range 4 - 8 months but is not reported for one patient. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | response to imiquimod with a high proportion of complete tumour resolution. Imiquimod 5% cream successfully treated 13 out of 17 BCCs in these patients with Gorlin's syndrome, with no patient suffering a relapse at the follow-up visit. | | |
| (Nouri *et al.* 2002) | To discuss the role of $CO_2$ laser therapy to treat BCC based upon a small series of patients. | Small case series study. | 3 patients with Gorlin's syndrome, and multiple, small, superficial BCCs and with age range 2-35 years.<br><br>**US** | Tumour response and recurrence. | After treatment with $CO_2$ laser the BCC tumour became erythematous plaques, noted at between 1 month and 6 months follow-up.<br><br>There was no evidence of recurrence or hypertrophic scarring at 18 months follow-up in any patient. Some minimal hypopigmentation or scarring was noted.<br><br>Author concludes that $CO_2$ laser therapy can treat multiple BCCs in a short period of time with minimal scarring. | Histological evaluation performed on randomly selected treated lesions by Mohs micrographic surgery. | 3 - |

# Transplant patients

### The questions

*What are the needs of transplant patients in terms of skin cancer services?*

### The nature of the evidence

Eleven studies were identified as follows:

- Two RCTs, of poor quality
- Three observational studies, one of good quality, one of fair quality and one of poor quality
- Two clinical guidelines of good quality
- Four expert reviews, two of good quality and two of poor quality

Two studies originate from the UK and two studies are from the US. One study was undertaken jointly in the US and Europe, one study was undertaken by a European collaboration and one study each originates from Holland, France, Ireland, Switzerland and Australia. Applicability to the UK is limited.

Ten studies are of patients who have received organ transplants, of which seven are of renal transplant patients. One study is based upon a survey of expert transplant physicians.

### Summary of the supporting evidence for the recommendations

### Incidence

**Evidence from observational studies and expert reviews suggests that transplant patients are at increased risk of skin cancer. This is believed to be due to the role of immunosuppressive drugs which are thought to be directly carcinogenic, with a further effect by causing a reduction in autoimmune surveillance and eradication of precancerous cells.**

**Observational study evidence suggests that skin cancer occurs at a rate of 141 per 1,000 person years at risk, based upon the number of years of exposure to immunosuppressant drugs. SCC is the most common post transplantation malignancy, occurring at younger age, with higher incidence of multiple tumours and increased aggressiveness than normally observed. Some patients develop more than 100 SCC lesions annually. Observational study evidence suggests that the mean time to presentation of the first skin cancer in transplant patients is 8 years. There is often a reversal of the ratio between SCC and BCC seen in transplant patients with skin cancer from that observed in the general population. The incidence of skin cancer increases with time since transplant and is higher in countries with Caucasian populations at low latitude.**

**Expert review evidence suggests that the increased risk of skin cancer in transplant patients is as follows:**

- **SCC: 65 fold**
- **SCC of the lip: 20 fold**
- **BCC: 10 fold**
- **Melanoma: 3.4 fold**
- **Kaposi sarcoma: 84 fold**

**The same level of evidence suggests that overall mortality from melanoma at 5 years is 30% in transplant patients compared with 15% in the general population. Child and adolescent transplant patients appear to have higher SCC and melanoma incidence than adults, with the mortality rate in paediatric transplant patients estimated as 8%.**

**There is also observational study evidence that transplant patients are at increased risk of appendageal tumours (those of apocrine, eccrine, pilar and sebaceous glands).**

**Risk factors**

**Evidence from observational studies, expert reviews and clinical guidelines suggests that risk factors for skin cancer in transplant patients are:**

- **long duration of immunosuppression and high intensity of immunosuppression: Bordea et al. (2004) found that immunosuppression extending over 5 to 10 years was associated with a four fold risk of skin cancer compared to less than five years immunosuppression, with risk increasing to almost 10 fold for immunosuppression lasting 10 years or more;**
- **intense immunosuppression;**
- **fair skin (Fitzpatrick types I-III), blue or hazel eyes, birth/residency in a hot climate, significant prior exposure to UV radiation, childhood sunburn;**
- **history of skin cancer or pre cancerous lesions at, or prior to, transplantation;**
- **recipient age at transplantation (higher risk for older and paediatric recipients);**
- **male gender;**
- **history of human papilloma virus (HPV) infection;**
- **older age;**
- **CD4 lymphocytopoenia.**

**Immunosuppressive drugs**

**Authors of observational studies report difficulty in evaluating the risk of skin cancer associated with individual immunosuppressive drugs, due to variability in regimens studied and since evidence quality is poor.**

**Observational study evidence suggests that recipients of azathioprine, irrespective of other agents, are at increased risk of SCC and recipients of cyclosporine, irrespective of other agents, are at increased risk of BCC. Treatment with prednisolone has been found to be associated with increased risk of SCC and BCC.**

**Expert review evidence suggests that patients treated with a combination of cyclosporine, azathioprine and corticosteroids (tritherapy) have a threefold risk of skin cancer compared to those treated with azathiaprine and corticosteroids (bitherapy).**

**Educational and Follow-up strategies**

**Authors recommend that transplant patients should be educated for self surveillance of skin and sun protection. Close dermatological follow-up is also recommended in one expert review as follows:**

- **No skin cancer: 12 monthly**
- **Actinic keratoses: 6 monthly**
- **Single melanoma: 6 monthly**
- **Multiple NMSC: 2 – 4 monthly**
- **High risk SCC/melanoma: 3 monthly**
- **Metastatic SCC/melanoma: 2 monthly**

**Chemoprophylaxis/treatment**

**Evidence from one RCT supports the use of photodynamic therapy (PDT) with methyl aminolaevulinate to treat actinic keratoses that arise in patients who have received organ transplants.**

**Observational study and clinical guideline evidence suggests that chemoprophylaxis with systemic retinoids may reduce the incidence of skin cancer. Topical retinoids have been found to reduce actinic**

**keratoses and SCC recurrence in transplant patients with little or no risk. One RCT which studied oral acitretin to treat actinic keratoses in transplant patients found that a low oral dose of 0.25 - 0.30 mg/kg/d reduces the number of actinic keratoses in renal transplant recipients but that patient tolerance should be considered due to side effects.**

**One clinical guideline recommends that warts, actinic keratoses and porokeratoses should be treated aggressively at the first development and where these lesions have an atypical clinical appearance or do not respond to therapy, a biopsy should be performed.**

**Reduction of immunosuppression**

**Authors of observational studies recommend that reduction in immunotherapy should be considered by transplant physicians for some patients in order to minimise the occurrence of skin cancers. Reducing immunotherapy remains unpredictable with a risk of death. One expert review suggests that reduction in immunotherapy should be considered at a threshold of 5 – 10 NMSCs, since approximately two thirds of transplant patients experience a reduction in incidence of cutaneous carcinomas after immunotherapy is stopped. Observational study evidence suggests that reducing or stopping immunosuppression may prolong metastatic disease free survival in renal transplant patients with aggressive SCC.**

**Multi disciplinary working**

**Authors stress the need for a multidisciplinary approach to therapeutically manage transplant patients with skin cancer, needing numerous surgical, transplant, oncology and radiological groups. One expert review suggests that closely integrated and well coordinated specialist clinics for dermatological management of transplant patients are highly effective.**

- The expert review by Berg and Otley (2002) reported that SCC is the most common post transplantation malignancy in transplant patients,

manifesting at younger age, with higher incidence of multiple tumours and increased aggressiveness compared to the general population. Risk factors include older (and paediatric) age, long duration of immunosuppression and intense immunosuppression.

- The retrospective case series study by Bordea et al. (2004) found the incidence rate of skin cancer in organ transplant recipients to be 141 per 1,000 person years at risk. 64 % of transplant patients with skin cancer had multiple lesions and SCC was the most common skin cancer to develop. The mean time to presentation of the first skin cancer was 8 years post transplantation and recipient age at transplantation was a highly significant risk factor for subsequent skin cancer development.

- The expert report based upon a survey of leading physicians undertaken by Christenson et al. (2004) recommended close follow-up of organ transplant recipients according to individual risk of skin cancer, education of patients on prevention of skin cancer and education of other care providers about the unique dermatological needs of transplant patients.

- The RCT comparing two doses of oral acitretin in renal transplant recipients undertaken by de Sevaux et al. (2003) concluded that oral acitretin reduces the number of actinic keratoses in this patient group, although the drug was poorly tolerated by patients.

- The RCT by Dragieva et al. (2004) compared topical photodynamic therapy with methyl aminolaevulinate (MAL) with placebo in the treatment of patients with actinic keratoses after organ transplant. The overall lesion complete response rate was 90% in the active treatment group and 0% in the placebo group ($p = 0.0003$).

- Evidence based guidelines produced by the EBPG Expert Group on Renal Transplantation (2002) recommend that patients should be educated about primary prevention of skin cancer and that transplant

recipients with pre-malignant skin lesions should be referred early to a dermatologist. Secondary prevention for recipients should include close follow-up by a dermatologist and treatments for skin cancer include topical retinoids, reduction of immunosuppression whenever possible and for multiple or recurrent skin cancer, systemic retinoids.

- The expert review by Euvrard, Ulrich, and Lefrancois (2004) found that transplant patients treated with a combination of cyclosporine, azathioprine and corticosteroids (tritherapy) as anti rejection therapy were found to have a threefold risk of skin cancer compared to those treated with azathiaprine and corticosteroids (bitherapy), although the authors reported that in general it was difficult to discern the individual roles of immunosuppressive drugs due to the many different regimens used.

- The retrospective case series study by Harwood et al. (2003) found that the occurrence of malignancy was significantly higher in transplant patients (43 %) compared with immunocompetent patients (4%, $p < 0.0001$) and suggested that the rate of cutaneous appendageal tumours in transplant patients is likely to be of similar order of magnitude to SCC. The authors recommended surveillance of organ transplant patients for appendageal skin tumours.

- The small, retrospective, case series study by Moloney et al. (2004) found that in 9 male renal transplant patients with aggressive SCC, reduction of immunosuppression was found to prolong metastatic disease free survival.

- The cross sectional study by Ramsay et al. (2003) found that in organ transplant patients, age at transplantation and duration of immunosuppression were significantly associated with increasing risk of NMSC. A dose response effect was notable, with 82.1% of patients in whom immunosuppression was of more than 20 years duration, developing skin cancer.

- Evidence based clinical guidelines produced by Stasko et al. (2004) recommended that patients in whom transplant is planned be given a skin examination and education for future skin cancer risk. Warts and premalignant lesions should be treated aggressively at the first development and SCC should be promptly managed with techniques including destructive modalities and excisional techniques. Aggressive SCC confined to skin and soft tissue should be managed promptly with complete removal by excisional techniques and reduction of immunosuppression should be considered in life threatening cases of SCC, or multiple SCC. The authors stressed the need for a collaborative approach, optimally including transplant physicians, dermatologists, oncology surgeons, pathologists, medical oncologists and radiation oncologists with experience of aggressive tumours in transplant recipients.

# EVIDENCE TABLE 6.5

***What are the needs of transplant patients in terms of skin cancer services?***

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Berg & Otley 2002) | To describe the epidemiology, clinical presentation and recommended management of skin cancer during post transplantation immunosuppression. | Evidence based Continuing Medical Education resource of the American Academy of Dermatology (144 references). | Transplant patients (populations from numerous countries in cited studies).<br><br>**Undertaken in the US** | Article addresses epidemiology, cofactors to accelerated carcinogenesis, preventive education and treatment of skin cancer. | SCC is the most common post transplantation malignancy in Caucasian populations and manifests with younger age at onset, higher incidence of multiple tumours and increased aggressiveness. Incidence of skin cancer increases with time since transplant and lower latitude, with increase in incidence as follows:<br><br>SCC: 65 fold<br>SCC of the lip: 20 fold<br>BCC: 10 fold<br>Melanoma: 3.4 fold<br>Kaposi sarcoma: 84 fold<br><br>Overall mortality from melanoma at 5 years is 30% in transplant patients compared with 15% in the general population.<br><br>Skin cancer can be particularly aggressive in child/adolescent patients with higher SCC/melanoma incidence than in adults. Paediatric transplant patients have a skin cancer mortality rate of 8%. Merkel cell carcinoma is also more aggressive in transplant patients than in the general population. A subset | Highly evidence based expert review.<br><br>Most data originates from the era of cyclosporine i.e. since 1979.<br><br>Role of immunosuppression is believed to be two fold: i) directly carcinogenic ii) causing reduction in autoimmune surveillance and eradication of precancerous cells.<br><br>The primary pathogenic factor both in transplant patients and the general population is UV light. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | of transplant patients develop > 100 SCCs annually.<br><br>Risk factors are older (and paediatric) age, long duration of immunosuppression, intense immunosuppression, fair skin, significant prior exposure to UV radiation, HPV infection, lower CD4 count, history of skin cancer prior to transplantation.<br><br>Education for self surveillance of skin and lymph nodes and sun protection is recommended although compliance has been found to be poor. Frequent dermatological follow-up is recommended according to risk:<br><br>No skin cancer: 12 monthly<br>Actinic keratoses: 6 monthly<br>Single melanoma: 6 monthly<br>Multiple NMSC: 2 – 4 monthly<br>High risk SCC / melanoma: 3 monthly<br>Metastatic SCC / melanoma: 2 monthly<br><br>Chemoprophylaxis with systemic retinoids may reduce the incidence of skin cancer. Topical retinoids have been found to reduce actinic keratoses in transplant patients with little or no risk. It is recommended that reduction in immunotherapy be considered when a threshold of 5 – 10 NMSCs is reached, coordinated by the transplant physician. This has been shown to reduce the risk of skin cancer but is associated with increased episodes of rejection and remains unpredictable with risk of death. Approximately two thirds of transplant patients experience a reduction in incidence of cutaneous carcinomas after immunotherapy is stopped. | | |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | The authors stress the need for a multidisciplinary approach to therapeutically manage transplant patients with skin cancer, needing numerous surgical, transplant, oncology and radiological groups. | | |
| (Bordea *et al.* 2004). | To provide a comprehensive epidemiologic review of skin cancers occurring in a population receiving renal transplants in Oxford over a 21-year period. | Retrospective analysis of a large case series. | 979 patients who developed skin cancer, out of 1115 renal transplant patients. Skin cancers were: BCC, Bowen's disease (BD), SCC, keratoacanthoma (KC), malignant melanoma (melanoma), Merkel cell tumour, and sebaceous carcinoma.<br><br>**UK** | Occurrence of skin cancer with analysis of risk factors. | 187 of 979 (19.1%) transplant patients developed at least one skin malignancy. 131 (70.1%) were males and 56 (29.9 %) were females. The rate of skin cancer was 141 per 1,000 person years at risk. 64 % of patients with skin cancer had multiple lesions (maximum 50). Rates of tumour types were:<br><br>SCC: 71.4/1000 py at risk<br>BD: 32.5/1000 py at risk<br>BCC: 22.4/1000 py at risk<br>KA: 9.26/1000 py at risk<br>melanoma: 0.53/1000 py at risk<br>Sebaceous carcinoma: 0.13/1000 py at risk<br>Merkel cell tumour: 0.13/1000 py at risk.<br><br>SCC was the most common skin cancer to develop (36.4 % of patients) and the most common first skin cancer to present. The ratio of SCC to BCC 3.2:1. The mean time to presentation of the first skin cancer was 8 years.<br><br>Six patients developed nodal metastases, and two patients died secondary to skin cancer. Recipient age at transplantation was a highly significant risk factor for subsequent skin cancer development (OR 1.07, 95 % CI 1.06 – 1.08, $p < 0.0001$).<br><br>Female recipients had a lower risk than males (OR 0.51, 95 % CI 0.37 – 0.69, p | Follow-up range 2 - 23 years.<br><br>Comparison of individual immunosuppressant drugs not carried out due to variation in regimens used.<br><br>No association with subsequent skin cancer development was found for cause of renal failure, type / length of dialysis, recipient blood group, smoking status, HLS mismatches, cold or warm ischemia time, number of acute rejection episodes, additional immunosuppression to treat rejection or any of the donor variables tested (age, gender, blood group, cytomegalovirus status). | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | < 0.0001). Patients with immunosuppression extending over 5 to 10 years were at four times the risk of skin cancer than those with less than five years immunosuppression, with risk increasing to almost 10 times for immunosuppression > 10 years.<br><br>Patients with creatinine > 150 µmol/L at 1 year had higher risk of skin cancer development (OR 1.74, 95 % CI 1.23 – 2.43, p = 0.001). The cumulative incidence of skin cancer reached 9 % at 5 years after transplantation, 27 % at 10 years and 61% at 20 years.<br><br>Author concludes: data from this study suggest that more patients develop skin malignancies than previously reported from Europe. It is important to advise patients before transplantation in regard to skin complications, provide regular dermatological follow-up, and tailor immunosuppressive regimen to minimum doses to be compatible with good graft function. | | |
| (Christenson *et al.* 2004) | To report on three types of speciality clinics, which are considered to be highly effective for proactive care. | Report based upon qualitative and quantitative survey of 12 physician members of the International Transplant Skin Cancer Collaborative (ITSCC). | Patient population is transplant patients. Survey was of physicians providing care.<br><br>**US / non UK European** | Measures recorded included: patients seen per week, referral scheme, timing of skin examinations, education methods, treatments provided, follow-up schema, research activities and extent (years) of experience. | The three clinic settings were:<br><br>i) Dermatology transplant sub-speciality clinic within a multidisciplinary transplant clinic<br>ii) Designated dermatology clinic for transplant recipients<br>iii) Clinical care of transplant recipients integrated into existing dermatology clinics.<br><br>The authors propose steps to providing the best care, based on this research:<br><br>• Close communication | Survey methods not reported. Graded as formal consensus evidence. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | between transplant physicians and nurse coordinators<br>• Education of other care providers about the unique dermatological needs of transplant patients<br>• Provision of an effective scheduling mechanism for seeing transplant patients in dermatology including baseline / triage assessment<br>• Education of patients on prevention<br>• Chemoprophylaxis<br>• Comprehensive dermatological care<br>• Close follow-up according to risk and as recommended in ITSCC follow-up guidelines<br>• Adherence to ITSCC guidelines for management of SCC<br>• Networking with other dermatologists via ITSCC email services and website. | | |
| (de Sevaux *et al.* 2003) | To compare maintenance doses of 0.2 (Low dose) and 0.4 (High dose) mg/kg/d of oral acitretin in the treatment of actinic keratoses in renal transplant patients. | RCT comparing two doses of oral acitretin. | Caucasian, adult renal transplant patients on a stable dose of immunosuppression, mostly with both prednisolone and azathioprine.<br><br>**Holland** | Number and aspect of actinic keratoses and the incidence of new tumours. Clinical and patients' reported parameters measured at baseline, week 2, months 1, 2, 3, 4.5, 6, 9 and 12 by the same investigator. | The average dose in both low and high dose groups was reduced due to poor tolerance, at 0.18 and 0.35 mg/kg/d respectively at month 3. In the high dose group the average dose reduced to 0.29 mg/kg/d at month 6. The dose remained significantly different between groups at all points.<br><br>Over the treatment period there was a similar incidence of SCC, BCC, Bowen's disease and keratoacanthoma. A rapid decrease in keratoses was seen in both groups beyond 2 months ($p < 0.0001$) with no difference between groups. No changes were seen in erythema scores. Lesion thickness decreased significantly | Small size.<br><br>In study recruitment author states preference for patients with at least 1 SCC and > 10 actinic keratoses.<br><br>No blinding ('open label').<br><br>In contrast to other studies, no reduction in the number of new tumours was observed. | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | in both groups (p less than or equal to 0.01). Patients' reported significant improvement in roughness of lesions (p = 0.002) and contentment (p = 0.001) after month 2.<br><br>Side effects noted dryness of lip, scaling of skin, temporary reduction in dryness of skin, nasal crusts, mild hair loss and brittle nails. Anaemia, urinary tract infections (in 3 female patients) and Achilles tendonitis were noted as possible new side effects.<br><br>The authors suggest that poor tolerance of acitretin in low dose may be linked to long term use of corticosteroids (c.f. dose for psoriasis) and recommend that for transplant patients with keratoses, 0.25 - 0.30 mg/kg/d be the initial dose, to be lowered or raised accordingly. Authors conclude that acitretin reduces the number of actinic keratoses in renal transplant recipients. | | |
| (Dragieva *et al.* 2004) | To evaluate the efficacy and tolerability of topical PDT with methyl aminolaevulinate (MAL) versus. placebo in the treatment of actinic keratoses in transplant recipients. | RCT<br><br>Intervention (n=17):<br>1mm thick topical application of MAL for 3 hours followed by 75 $Jcm^{-2}$ of visible light at 80$mWcm^{-2}$ with a spectrum of 600-730nm.<br><br>Control (n=17):<br>As above, but with placebo cream.<br><br>Two treatments were given, one | 17 transplant patients (13 kidney, 4 heart) with a total of 129 actinic keratosis lesions.<br><br>Mean age 61 (range 44-76) years.<br><br>**Switzerland** | Proportion of lesional areas with complete response (CR), partial response (PR) or no response (NR), evaluated at weeks 4, 8 and 16 after treatment. | At 16 weeks follow up, CR was seen in 13 (95% CI 9-16) of 17 patients treated with MAL with a PR in a further 3 and NR in one patient.<br><br>NR was seen in all placebo-treated areas.<br><br>The overall lesion complete response rate was 56 of 62 for treatment of fields with PDT with MAL and 0 of 67 for treatment of fields with PDT with placebo (p = 0.0003).<br><br>Adverse events, such as erythema, oedema and crust formation, were mild to moderate, and treatment was well tolerated by all patients. | Randomisation was by treatment field. There were 2 treatment fields in each of 17 patients, but it is not clear whether each patient received MAL and placebo, or just one or the other.<br><br>Trial was double blinded.<br><br>Small sample size, but adequate power calculation performed. | 1 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | week apart. | | | | | |
| (EBPG Expert Group on Renal Transplantation. 2002) | To provide evidence based guidelines for the care of renal transplant patients. | Evidence based guidelines. | Renal transplant patients.<br><br>**Produced by a European collaboration** | Recommendations for practice. | Recommendations are as follows:<br>• Due to the high prevalence of skin cancers after organ transplantation, it is highly recommended to inform patients about self-awareness.<br>• Primary prevention should include the avoidance of sun exposure, use of protective clothing and use of an effective sunscreen (protection factor >15) for unclothed body parts (head, neck, hands and arms) in order to prevent the occurrence of squamous-cell carcinoma. This is the most frequent skin tumour in transplant recipients, and its preferential location is the head.<br>• Recipients with pre-malignant skin lesions (warts, epidermodysplasia verruciformis or actinic keratoses) should be referred early to a dermatologist for active treatment and close follow-up.<br>• All skin cancers should be completely removed by a dermatologist with appropriate techniques, such as electro-desiccation with curettage, cryotherapy or surgical excision.<br>• Secondary prevention for recipients should include close follow-up by a dermatologist (at least every 6 | Only extract available for review. Extensive references provided and recommendations graded accordingly, but no details of methodology available. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | months), the use of topical retinoids to control actinic keratoses and to diminish squamous-cell carcinoma recurrence, and reduction of immunosuppression whenever possible.<br>• In recipients with multiple and/or recurrent skin cancers, the use of systemic retinoids, such as low-dose acitretin, could be recommended for months/years, if well tolerated, in addition to further reduction in immunosuppression whenever possible. | | |
| (Euvrard *et al.* 2004) | To review studies reporting the role of commonly used immunosuppressant drugs with regard to development of skin cancer. | Expert review. | Transplant patients, although many studies cited are based upon experiments conducted on mice.<br><br>**France** | Authors discuss pathogenic or protective roles of drugs with regard to skin cancer. | OKT3 has not been consistently shown to be associated with skin cancer. Corticosteroid evidence comes from non transplant patients, for whom risk of SCC is increased and also modestly, risk of BCC.<br><br>Patients treated with a combination of CsA, azathioprine and corticosteroids (tritherapy) were found to have a threefold risk of skin cancer compared to those treated with azathiaprine and corticosteroids (bitherapy).<br><br>The risk of skin cancer from tacrolimus relative to that from CsA is unknown.<br><br>No information was available for Mycophenalate Mofetil on skin cancer risk.<br><br>Clinical evidence suggests that Sirolimus (Rapamune) may confer a benefit in terms of skin cancer risk over CsA. The authors conclude that whilst more research is needed on Sirolimus, | Authors note difficulty in discerning individual roles of immunosuppressive drugs due to regimens used. | 4 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | a switch to sirolimus may be considered for transplant patients on CsA who have developed SCC. | | |
| (Harwood *et al.* 2003) | To examine cutaneous appendageal tumours arising in recipients of renal transplants compared with immunocompetent individuals. | Retrospective case series study (single centre) identifying tumours of interest from a histopathology database reported over a 6 year period. | Patients with appendageal tumours i.e. tumours of apocrine, eccrine, pilar and sebaceous gland origin.<br><br>Incidences occurred within a population of 605, 000 people served by the hospital.<br><br>**UK** | Primary comparison is between renal transplant patients and immunocompetent patients; with very few numbers seen of other groups i.e. patients with immunosuppressive medical conditions and Muir Torre Syndrome. | 231 appendageal tumours were included in the analyses. 23 of these occurred in 21 of 650 (3 %) renal transplant patients cf. 195 in 178 apparently immunocompetent patients.<br><br>Malignancy was significantly over-represented in transplant patients (43 %) cf. immunocompetent (4%), ($p < 0.0001$).<br><br>Sebaceous tumours were also over represented in transplant patients compared with immunocompetent patients (30 % vs. 6 %, $p < 0.0001$).<br><br>The authors suggest that the rate of cutaneous appendageal tumours in transplant patients is likely to be of similar order of magnitude to SCC.<br><br>At follow-up of mean 3.5 years for transplant and 4.2 years for immunocompetent patients, prognoses remained generally good after complete surgical excision.<br><br>Author suggests surveillance of organ transplant patients due to high frequency, diversity and indolence of tumours observed. | Study excluded sebaceous gland hyperplasia, extra mammary Paget's disease and appendageal nevi / haematomas.<br><br>Tumours also occurred in patients with immunosuppressive medical conditions and Muir Torre Syndrome. | 3 - |
| (Moloney *et al.* 2004) | To determine the effect of significantly reducing or stopping immunosuppression on time to detection of metastases in renal transplant patients with aggressive SCC. | Small retrospective case series.<br><br>Patient demographics, skin cancer and transplant related histories were reviewed. | 9 male renal transplant patients with aggressive SCC.<br><br>**Ireland** | Time to distant metastases. | 5 patients received no change in immunosuppressive therapy and 4 patients had immunosuppressive therapy stopped or significantly reduced.<br><br>The two groups were demographically similar. 6 patients developed metastatic SCC at mean 9 months following initial | Intended as a small pilot study.<br><br>8 patients were receiving triple immunosuppression of cyclosporine, azathioprine and prednisolone and 1 patient (with a living related donor) received azathioprine only. | 3 - |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | Histology review recorded tumour characteristics. | | | aggressive SCC diagnosis (range 5 - 17 months). 3 patients developed no further metastases during the follow-up period of 13 to 27 months, one of whom returned to dialysis. Median (follow-up) time to metastases or end of study was 23 months in the 'withdrawal' group versus 6 months in the 'no change' group ($p = 0.027$).<br><br>The authors conclude that reducing or stopping immunosuppression may prolong metastatic disease free survival in renal transplant patients with aggressive SCC and should be considered for such patients. | | |
| (Ramsay *et al.* 2003) | To determine clinical and environmental factors associated with post - transplantation NMSC in Queensland. | Quantitative cross sectional study based upon structured interview, transplant history and full skin examination. | 361 Caucasian renal transplant recipients aged 16 or over living in Queensland, Australia, with Fitzpatrick skin types I to IV.<br><br>**Australia** | Occurrence of SCC and BCC used as end points with OR calculated for many demographic, clinical and environmental exposure data. | 3979 histologically proved NMSCs developed in 187 (51.8 %) patients after transplantation: 1817 invasive SCCs in 135 patients, 1012 Bowen's disease in 121, 916 BCCs in 143 and 227 keratoacanthomas in 61 patients.<br><br>Age at transplantation and duration of immunosuppression were significantly associated with increasing NMSC risk and numbers; 29.1%, 52.2%, 72.4% and 82.1% who underwent immunosuppression for < 5, 5 – 10, 10 – 20 and > 20 years, respectively developed NMSC.<br><br>The presence of both SCC and BCC prior to transplantation was significantly associated with increased risk and numbers of NMSC. Actinic keratoses at or before the time of transplantation were significantly associated with NMSC risk and numbers.<br><br>Detailed immunosuppression data were available for 274 (76%) of the 361 | The distribution of skin cancer was reported in a previous study. All analyses were corrected for age at transplantation, gender and duration of immunosuppression.<br><br>Study reports many individual risk factors with OR and 95% CIs. Mainly transplant related factors cited herein. | 3 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | | | | | patients. Recipients of azathioprine, irrespective of other agents, were at increased risk of SCC (OR 2.4, p = 0.019). Recipients of cyclosporine, irrespective of other agents, had an increased risk of BCC (OR 4.1, p = 0.002). Treatment with prednisolone was associated with increased risk of SCC (OR 3.9, p = 0.001) and BCC (OR 3.2, p = 0.002). No significant associations were found between NMSC risk or numbers and the number of transplantations, donor source, cause of renal disease or HLA mismatch.<br><br>SCC was strongly associated with fair skin, blue or hazel eyes, time resident in a hot climate, and pretransplantation SCC; tumour numbers were associated with birth in a hot climate, childhood sunburn, pretransplantation actinic keratoses, and smoking.<br><br>The risk of BCC was strongly associated with acute or intermittent sun exposure during childhood and pretransplantation BCC; numbers were associated with blue or hazel eyes, time spent living in a hot climate, and male gender.<br><br>The authors conclude that clinical and environmental factors can be used to identify recipients at risk of NMSC in Queensland and that BCC and SCC have independent pathogeneses and should be considered separately for risk. | | |
| (Stasko *et al.* 2004) | To develop useful clinical guidelines for the treatment of skin cancer in organ transplant | Evidence based clinical guideline. | Organ transplant recipients.<br><br>**US** | Recommendations provided. Literature research and guideline | **Screening and Education:** Patients should be given a skin examination prior to transplantation and be educated regarding future skin cancer risk. All | 63 references cited. Appraised using 'AGREE' tool. | 4 ++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | recipients. | | | development process not fully reported. | organ transplant recipients are considered to be at increased risk of skin cancer, however within this group factors for higher susceptibility include:<br><br>• History of skin cancer<br>• History of actinic keratoses<br>• Fair skin (Fitzpatrick types I-III)<br>• History of chronic sun exposure / sun burn<br>• Older age<br>• Duration and intensity of immunosuppression<br>• History of human papilloma virus (HPV) infection<br>• CD4 lymphocytopoenia<br><br>**Warts and premalignant lesions:**<br><br>• Warts, actinic keratoses and porokeratoses should be treated aggressively at the first development.<br>• Where these lesions have an atypical clinical appearance or do not respond to therapy, a biopsy should be performed.<br><br>**Evaluation and management of SCC:**<br><br>• All transplant recipients with suspected or proven SCC should have a thorough pre-treatment evaluation.<br>• Less aggressive SCC should be promptly managed with techniques including destructive modalities and excisional techniques. Histology should be obtained on all lesions.<br>• Aggressive SCC confined to | | |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | skin and soft tissue should be managed promptly with complete removal by excisional techniques.<br>• Satellite lesions require additional therapy and evaluation.<br>• Where SCC leads to palpable lymphadenopathy or extensive spread, transplant patients should be treated as non-immunosuppressed patients with additional attention to reduction in immunosuppression and chemoprophylaxis.<br>• Decreasing immunosuppression should be considered in life threatening cases of SCC, or multiple SCC, by consultation with the transplant physician.<br><br>**Collaborative approach:**<br><br>• A collaborative approach is required, optimally including transplant physicians, dermatologists, oncologic surgeons, pathologists, medical oncologists and radiation oncologists with experience of aggressive tumours in transplant recipients. | | |

# Children with skin cancer

### The question

*To what extent are children and adolescents with skin cancer recruited into clinical trials?*

### The nature of the evidence

The evidence base underpinning service configuration for the support of children and young people with cancer has been reviewed in the NICE Cancer Service Guidance on Improving Outcomes in Children and Young People with Cancer.

Evidence for the role of clinical trials in patients with skin cancer was reviewed in Chapter two, 'Patient centred care'. In the current section evidence is reviewed on the extent to which children and adolescents with skin cancer are included in clinical trials.

Sixteen studies were identified as follows:

- One systematic review of high quality
- Two observational studies, one of good quality and one of fair quality
- One clinical guideline of good quality
- Four expert reviews, three of good quality and one of fair quality
- Eight expert opinion sources (discussion papers, essays, letters)

Eight studies originate from the UK and five are from the US. One study was produced jointly in the UK/US, one jointly in the UK/Italy and one is from Canada. Applicability to the UK is reasonable, but limited.

Thirteen studies relate specifically to children in clinical trials (and commonly children with cancer), of which one is of children and adolescents with melanoma. Two studies are of patients with cancer, including children and the

systematic review addresses populations of patients treated within RCTs, including children.

**Summary of the supporting evidence for the recommendations**

**Evidence from observational studies suggests that adolescents do not have equal access to trials as either adults or children.**

**A systematic review which investigated patient outcomes between participants and non participants (including children and adults) in randomised controlled trials found little evidence for better outcomes or greater risks, through participation in trials. An expert review found little generalisable evidence to support the contention that trial participation directly improves outcomes.**

**One expert review noted that although cancer in childhood and adolescence is rare, melanoma in adolescence is more common than in childhood and that adolescent patients with melanoma are under-represented in clinical trials and that trials often fail to address the age specific aspects of melanoma in adolescents.**

**Expert opinion reports that it is difficult to recruit sufficient numbers of children with cancer into trials which evaluate the efficacy of novel treatments, with the effect that novel treatments become widely used without mature evidence to support their efficacy.**

- The systematic review by Vist et al. (2004) concluded that participation in RCTs is not associated with greater risks than receiving the same treatment outside RCTs.

- The retrospective analysis by Liu et al. (2003) found that the annual age-adjusted registration rate in clinical trials was 71% for children aged under 15years, 24% for adolescents aged 15-19 years, and 57% for adolescents aged 19 - 20 years.

- The descriptive study by Bleyer et al. (1997) found that older adolescent subjects (aged over 14 years) were universally under-

represented in clinical trials, in both children and adult trial centres, regardless of ethnicity.

- The expert review by McTiernan (2003) concluded that adolescents do not have equal access to trials.

- The expert review by Pappo (2003) reported that melanoma preferentially affects adolescents over children but that adolescents are underrepresented in clinical trials and that studies fail to stage melanoma accurately in children and adolescents.

- The expert review by Stiller (1994) reported that for children with acute lymphoblastic leukaemia, trial entry had no effect on outcome at high volume centres. Trial effect was demonstrated in children with Wilms tumours.

- The expert review by Peppercorn et al. (2004) concluded that children are over represented in positive trials although there is little generalisable evidence that participation in trials improves outcome.

- The expert opinion paper Ablett, Pinkerton, and the United Kingdom Children's Cancer Study Group (2003) concluded that recruitment of children into clinical trials is low for some types of tumour e.g. brain tumours, as is recruitment of adolescents.

- Clinical guidelines by Mcintosh et al. (2000) support and encourage research involving children.

- The expert opinion paper by Pratt (1991) reported difficulty in recruiting adequate numbers of children with rare cancers in trials to determine response rates to drugs and stated the case for research on children's behalf.

- The expert opinion paper by Pinkerton et al. (2002) reported that difficulty in recruiting large numbers of children with cancer into trials leads to the acceptance of novel treatments as standard without supportive evidence.

- The expert opinion paper by Devine (2001) argued in favour of terminally ill children being involved in decisions to participate in trials.
- The expert opinion paper by Choonara (2000) recommended financial incentives for pharmaceutical companies to conduct trials of medicines in children.
- The expert opinion paper by Ault (2004) urged caution in offering financial incentives to pharmaceutical companies for trials in children.
- The expert opinion paper by Bonati, Impicciatore, and Pandolfini (2000) called for a register of trials in children to inform patients and parents of clinical trials in progress.
- The expert opinion paper by Kauffman (2000) argued that the US incentive for pharmaceutical companies developing drugs for licensing in children would create further child research interest internationally and that many trial protocols previously employed in adult studies would not translate to studies in children for ethical and efficacy reasons.

# EVIDENCE TABLE 6.6

## *To what extent are children and adolescents with skin cancer recruited into clinical trials?*

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| (Ablett *et al.* 2003) | To discuss issues related to children in clinical trials in the UK. | Expert opinion. | Children with cancer ≤ age 15 years.<br><br>**UK** | | Author concludes:<br>• Referral into specialist centres for children with cancer and recruitment into trials is very high and exceeds the targets currently being set for the NCRN for adult cancer trials in the UK.<br>• Recruitment is low in children with e.g. brain tumours and adolescents.<br>• There is also geographical variation in centre facilities which may lead to differences in recruitment.<br>• Issues remain about randomisation rates to certain studies compared with European centres. | | 4 |
| (Ault 2004) | To discuss the governance of clinical research involving children. | News article - expert opinion. | Children in clinical trials.<br><br>**US** | | Reports that the US Institute of Medicine (IOM) recommends that federal rules designed to protect children in clinical trials should be extended to cover all studies. The article reports on criticism of the financial incentive made available to pharmaceutical companies in the form of extended patents for the development of drugs for children. | | 4 |
| (Bleyer *et al.* 1997) | To evaluate whether adolescents (aged 15-19) | Descriptive Study - Trial inclusion data | Subjects under 20 years of age in trials | Proportion of registered cancer | Younger children (0-14 years) had equal access to clinical trials to other age | Trial inclusion data for CCG and POG were provided by a | 3 + |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | have equal access to clinical cancer trials as compared to children (aged 0 to 14). | from two major treatment affiliations were compared between the two age groups. The 'expected' distribution of trial inclusion in these groups was generated using routine surveillance data. Geographical and ethnic factors were also considered. | affiliated with the Children's Cancer Group (CCG) and Paediatric Oncology Group (POG), with the reference population data provided by the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute (NCI).<br><br>**US** | cases by age group recruited onto clinical trials. | groups. Older adolescent subjects were universally under-represented in clinical trials, in both children and adult trial centres, regardless of ethnicity. | previous comparative study. | |
| (Bonati *et al.* 2000) | To argue for a register of clinical trials for the benefit for child participants and their parents. | Letter - expert opinion. | Children in clinical trials.<br><br>**Italy/UK** | | Author calls for a register of clinical trials in children, stating that trials are seldom carried out in paediatric patients and that subsequently many children receive drugs that are not labelled for paediatric use. It is argued that registries facilitate patients' and parents' access to and recruitment into trials and provides all of the available evidence on trials in which they may participate. | | 4 |
| (Choonara 2000) | To discuss difficulties arising from a lack of paediatric drug trials. | Expert opinion – Letter to Journal. | Children in trials evaluating drugs.<br><br>**UK** | | Discusses the difficulties that arise from a lack of clinical trials of medications in children. Recommends that the UK and Europe make financial incentive for the pharmaceutical industry to study medicines in children, such that effective and safe medicines are made available to clinicians. | | 4 |
| (Devine 2001) | To argue in favour of a terminally ill child's full participation in the decision to enter into phase I and phase II clinical trials. | Argument essay. | Relates to terminally ill children.<br><br>**UK** | | Recommends that a formal study be undertaken of the role of the child in clinical trials and that children are actively rather than passively entered into clinical trials. | Discussion/opinion article. | 4 |
| (Kauffman 2000) | To argue that agencies involved with trial in children must work to | Argument essay. | Children involved in clinical trials. | | Author notes the 6 month extended market exclusivity for drugs developed for license in children. It is argued that | Expert opinion | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | ensure that future research is ethically and scientifically rigorous. | | **US** | | this measure will create further child research interest internationally and that many protocols employed in adult studies will not translate to studies in children for ethical and efficacy reasons. | | |
| (Liu *et al.* 2003) | Retrospective analysis. | Analyses of Children's Oncology Group (COG) to determine whether it would serve as a resource for identifying children with cancer. | 10,108 children <20 years old with cancer, identified by the 11 SEER registries between 1992-1997.<br><br>**US** | Trial registration rates. | Not all children are registered by the cooperative groups. The annual age-adjusted registration rate (AARR) was 71% for children <15 years, 24% for adolescents 15-19 years, and 57% for children <20 years. Registration rates varied by geographic region and were higher among children with advanced disease. Registration rates were highest for children (<15 years) with leukaemia (84%), hepatic tumours (82%)and renal tumours (80%) and were lowest for carcinoma (26%) and retinoblastoma (30%). | Confirms UK studies of low registration for older children and adolescents and differences with tumour type. | 3 |
| (McIntosh *et al.* 2000) | To provide guidelines to those involved in research with children. | Guidelines. | Children are defined by law as those under 18 years.<br><br>**UK** | | In terms of accessibility of trials the guidance states that :<br>• Research involving children should be supported and encouraged<br>• Research should only be done on children if comparable research on adults could not answer the same question and older children should be used in preference to younger ones<br>• It is important to validate in children the beneficial results of research conducted in adults<br>• Research that is of no intended benefit to the child subject is not necessarily unethical or illegal<br>• High risk procedures are not justified for research purposes alone. | Guidelines. | 4 ++ |
| (McTiernan 2003) | Consideration of issues about participation of adolescents in trials. | Expert review. | Adolescents (aged 15 -19 years) with cancer.<br><br>**UK** | | Author concludes:<br>• Clinical trials imperative to improve treatment and prognosis.<br>• Adolescents do not have equal access to trials due to | Age definition of adolescents not provided. | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
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| | | | | | fragmentation of care between paediatric and adult settings.<br>• Compliance is less in adolescents and needs research. | | |
| (Pappo 2003) | To report on epidemiology, risk factors, clinical presentation and treatment of melanoma in children and adolescents. | Report based upon literature review of case series reports. | Children and adolescents with melanoma.<br><br>**Canada** | Various: incidence, prevalence of melanoma and associated traits. Most studies report survival. | Author concludes:<br>• Melanoma preferentially affects adolescents over children but is underrepresented in clinical trials.<br>• Studies fail to stage melanoma accurately in children and adolescents and do not use the AJCC model.<br>• Sentinel node biopsy should be studied in children and adolescents for comparison with evidence on adults.<br>• There are no prospective trials of non surgical therapies in children and adolescents.<br>• International investigators have highlighted the need to overcome obstacles to studying rare tumours in children and adolescents. | Literature review. | 4 + |
| (Peppercorn *et al.* 2004) | To compare in cancer patients outcomes between trial participants and patients treated off protocol. | Literature review of 24 studies which compared outcomes between trial and non-trial patients. A conceptual framework was created to assess the studies. | Numerous populations of patients with different cancer types, including studies of children (which were over represented).<br><br>**UK/US** | The review reports on study inclusion criteria, study characteristics, control of baseline imbalances and trial effects. | 14 out of 26 comparisons provided some evidence that patients who enrol in trials have improved outcomes. Children were one of three groups disproportionately represented in positive studies. However strategies to control for confounding factors were frequently inadequate and the review found little generalisable evidence to support the contention that trial participation directly improves outcomes for cancer patients and recommends that recruitment messages should focus on the unquestioned contribution of trials to improving the treatment of future patients. | No meta analyses carried out due to concerns with biases in the primary studies. | 4 ++ |
| (Pinkerton *et al.* 2002) | To compare ethical approval systems in the UK, Germany and France and to discuss | Discussion paper. | Children involved in clinical trials.<br><br>**UK** | | Author notes that even in common tumours that occur in children, small patient numbers mean that phase III trials are inadequately powered to | Expert opinion. | 4 |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | moves towards a more standard approach. | | | | provide reliable results. Author cites a EU directive which states 'Medicinal products including vaccines for children need to be tested scientifically before widespread use.' | | |
| (Pratt 1991) | To describe the protocols of phase I and II therapeutic clinical trials in children with cancer at a US cancer centre and to discuss ethical issues. | Expert opinion. | Children with cancer (not melanoma).<br><br>**US** | | The National Cancer Institute of the US does not permit phase I trials of drugs in children until after the maximum tolerated dosage has been determined in adults. It is difficult to accrue adequate numbers to determine response rates to drugs in children with uncommon cancers. The author argues for research on children's behalf and for enrolling every available patient. | Expert opinion. | 4 |
| (Stiller 1994) | To review the published literature on survival rates for cancer in relation to organisation of services, specifically treatment at specialist centres or at hospitals treating larger numbers of patients and treatment within clinical trials. | Expert review. | Patients with cancer.<br><br>**UK** | Survival. | For children with acute lymphoblastic leukaemia (ALL) there was a significant trend towards higher survival rates in children being treated at high volume centres. Children entered into MRC trials had a significantly higher survival rate. Trial entry had little effect on survival at high volume centres.<br>For children with non leukaemia cancers entry to a trial and treatment at a teaching hospital were both associated with a higher survival rate.<br><br>In 2 studies of children with retinoblastoma survival rate was highest at the national referral centre.<br>For children with Wilms tumour survival rates were highest for those included in MRC trials than those who were eligible but not included. Patients, who had surgery at a specialist centre had higher survival rates. | The papers are not critically appraised. The author discusses the possible sources of bias. Other possible outcome measures are discussed.<br><br>Review of published literature from 1984-1993 (Medline, Embase) on patterns of care. | 4 + |
| (Vist *et al.* 2004) | To assess the effects of patient participation in RCTs ('trial effects) independent of both the effects of the clinical | Systematic review. | Review included 5 randomised studies (patients were randomised to be invited to participate | Mortality, morbidity and clinically important changes in outcomes measured on | Randomised studies: None of these 5 studies found statistically significant differences in outcomes of patients treated within and outside of RCTs. Quantitative synthesis was not | | 1++ |

| STUDY | AIMS | DESIGN | POPULATION | OUTCOMES | RESULTS | COMMENTS | Level |
|---|---|---|---|---|---|---|---|
| | treatments being compared, and any differences between patients who participated and those who did not. | | in an RCT or not) and 50 non-randomised cohort studies. Included a total of 31140 patients treated in RCTs and 20380 treated outside RCTs. Review included comparisons of the following interventions: surgery (27), drugs (22), radiotherapy (14), counselling (8), usual care (9) and active monitoring (8). Clinical specialties of the included studies: oncology (28), cardiology (13), obstetrics and gynaecology (15), psychology (9) and paediatrics (8).<br><br>**Review undertaken in the UK** | continuous scales (such as pain and complication rates). | conducted because of heterogeneity in research design.<br><br>Cohort studies: There was statistically significant heterogeneity among the 73 dichotomous outcome comparisons ($p < 0.01$, $I2=89.0\%$). In 59 of the 73 comparisons reported, no significant differences in outcomes were found. 10 comparisons reported statistically significant better outcomes for patients treated within RCTs, and four comparisons reported statistically significant worse outcomes for patients treated within RCTs.<br><br>Sub group analyses were carried out for different types of treatment (surgery, chemotherapy, etc.), for different clinical areas (oncology, cardiology, etc.) and for the different reasons patients refused to participate in the RCT (treatment preference etc.). None of these sub group analyses helped explain the heterogeneity in the overall analysis (statistical results of subgroup analyses were not included in the review).<br><br>Authors' conclusions: This review indicates that participation in RCTs is not associated with greater risks than receiving the same treatment outside RCTs. These results challenge the assertion that the results of RCTs are not applicable to usual practice. | | |

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# Appendix A

# An assessment of need for cancer services for skin cancer patients in England and Wales

## A report to the National Collaborating Centre for Cancer

Dr. Jat Sandhu and Dr. Julia Verne

# 1. Epidemiology of skin cancers

Skin cancers are the most common malignant tumours diagnosed in the UK with approximately 60,000 new cases registered in England and Wales each year, accounting for 20% of all cancer registrations. While this figure is acknowledged to be a gross underestimate there is general agreement that the incidence of all types of skin cancer is steadily increasing due to social changes such as increased sun exposure.

The National Collaborating Centre for Cancer has been commissioned to prepare service guidance for the NHS in England and Wales for cancers of the skin. To aid the guidance development process a needs assessment was conducted to provide an overview of the descriptive epidemiology and current patterns of service provision for patients with skin cancers.

There are many types of skin cancer, but three types are responsible for more than 95% of all skin cancers. They are Basal Cell Carcinoma (BCC), Squamous Cell Carcinoma (SCC) and Malignant Melanoma (melanoma) [Table 1].

**Table 1. Skin cancer registrations, incidence and mortality, England and Wales, 2001**

| Type | Registrations | Incidence Rate per 100,000 | Deaths | Mortality Rate per 100,000 |
|---|---|---|---|---|
| | 2001 | 2001 | 2001 | 2001 |
| **Melanoma** | | | | |
| Male | 2802 | 10.1 | 755 | 3.0 |
| Female | 3620 | 11.7 | 716 | 2.6 |
| All Persons | 6422 | 10.9 | 1471 | 2.8 |
| **Non-Melanoma** | | | | |
| Male | 26871 | 96.3 | 218 | 0.9 |
| Female | 23523 | 64.9 | 183 | 0.7 |
| All Persons | 50394 | 80.6 | 401 | 0.8 |

Cancer registrations and deaths from ICD10 C43-C44, ICD9 172-173.

## 1.1 Melanoma

Malignant melanoma, although far less prevalent (around 10% of skin cancers) than NMSC, is the major cause of death (about 80%) from skin cancer and is more likely to be reported and accurately diagnosed than NMSC.

Age standardised incidence increased through the 1970s to 1990s, reaching a peak in 2001, with rates being 11.7 (females) and 10.1 (males) per 100,000 population [Figure 1].

The incidence of melanoma increases with age in both males and females rising steadily in both sexes from age 15 years onwards. In 2001 incidence peaked at 49 in males and 30 in females per 100,000 population in those aged 85 years and over [Figure 2].

Examining for cohort effects in the past two decades, the incidence of melanoma continues to increases with age, peaking in those in the oldest age groups but the

incidence has also progressively increased in each age group over the age of 20. [Figure 3].

The age specific mortality rates for melanoma of the skin are similar for both men and women, and the numbers mirror the increase in incidence with increase in age. The 2001 provisional figures indicated that the peak mortality at ages 85 years and over reached 20 in males and 15 in females per 100, 000 population [Figure 4].

Male mortality rates from skin melanoma has risen steadily since the 1970s with more than doubling in by 2001 (1.0/100,000 in 1970, 2.6/100,000 in 1999). Mortality in females increased across the same time period, but to a smaller extent (from 1.4/100,000 to 2.0/100,000 population) [Figure 5].

While age specific mortality rates for melanoma peak in the oldest age groups, there appears to be an increasing mortality rate over the past two decades that is particularly discernible in the over 60 age groups [Figure 6].

Survival of melanoma patients has improved over time. Consistent with the mortality rates seen, survival among melanoma patients decreases with increasing age and is lower among males [Figure 7]. Of patients diagnosed with melanoma between 1991 and 1995, one-year survival in those aged over 80 was 85% for males and 90% for females, while five-year survival in the same age group was 59% for males and 69% for females.

**Figure 1. Age standardised incidence of melanoma, England and Wales, 1971–2001**

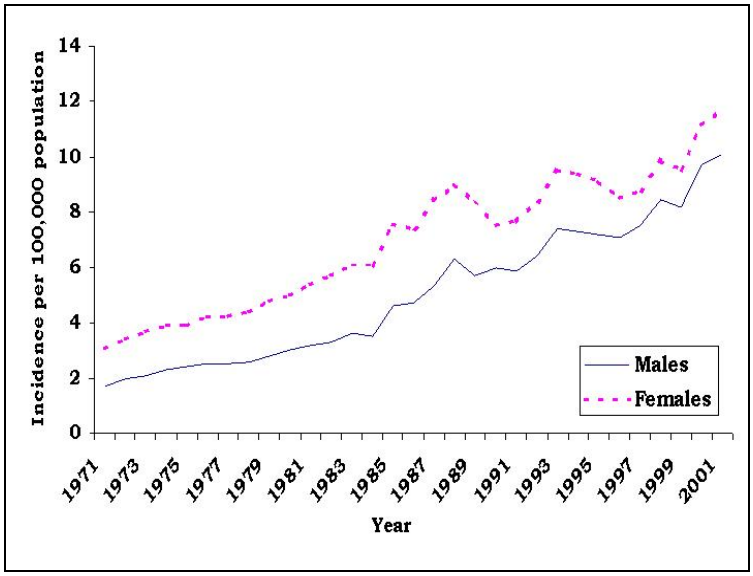



**Figure 2. Age Specific Incidence of melanoma, England and Wales, 2001**

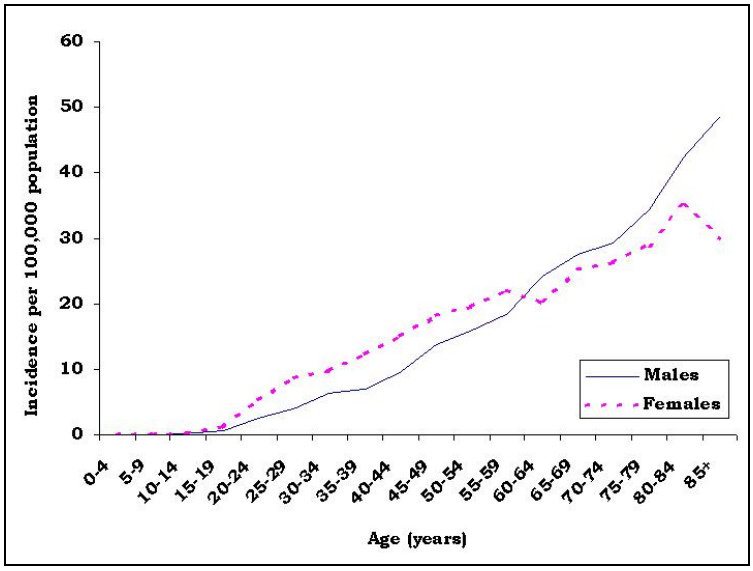


**Figure 3. Age Specific Incidence of melanoma, England and Wales, 1981 - 2001**

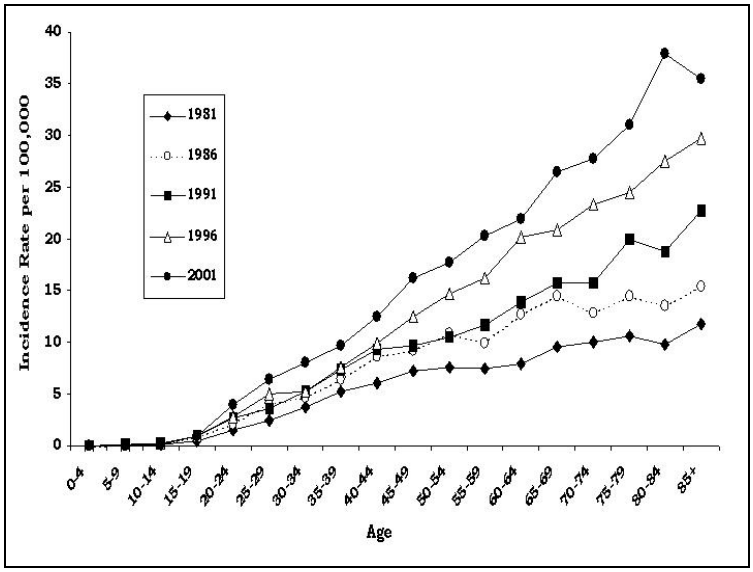



**Figure 4. Age Specific Mortality from melanoma, England and Wales, 2001**

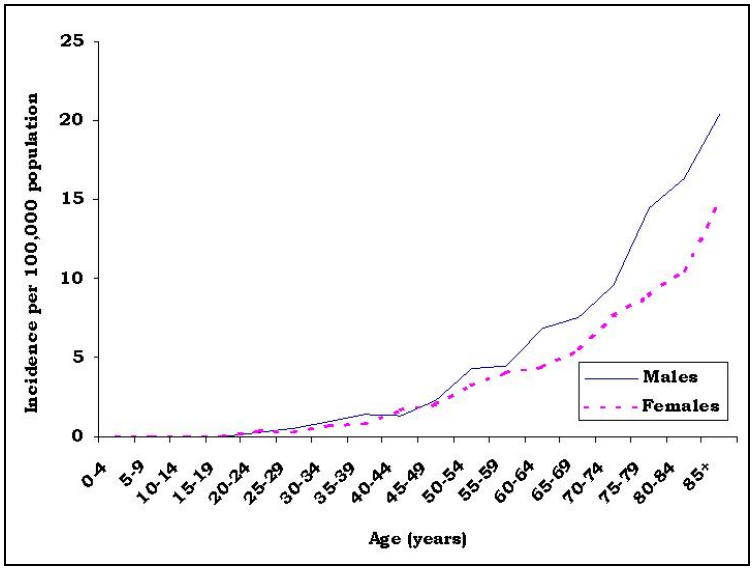


**Figure 5. Age standardised mortality from melanoma, England and Wales, 1971-2001**

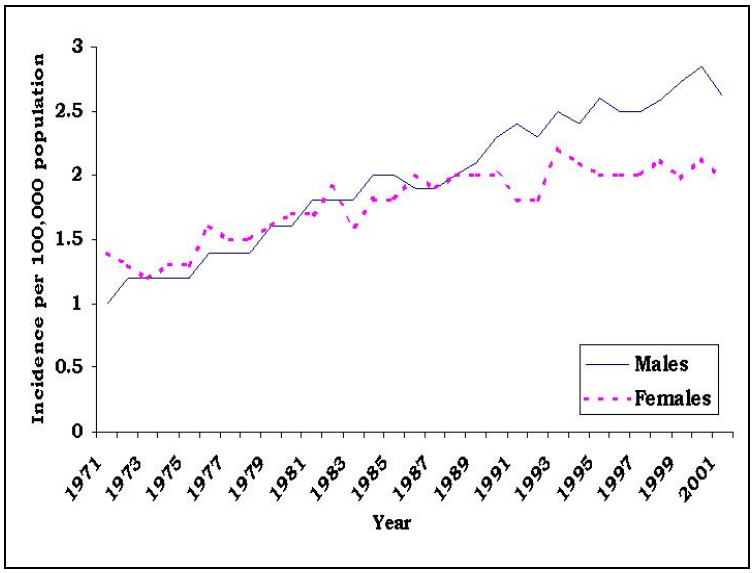
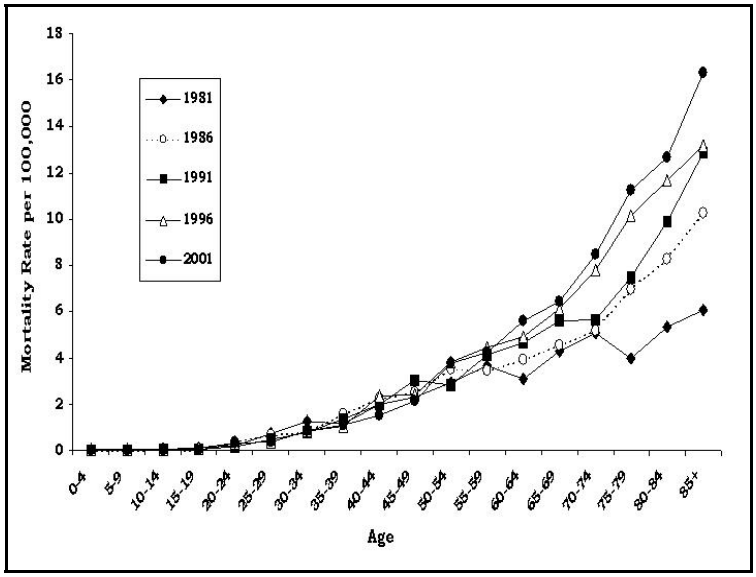
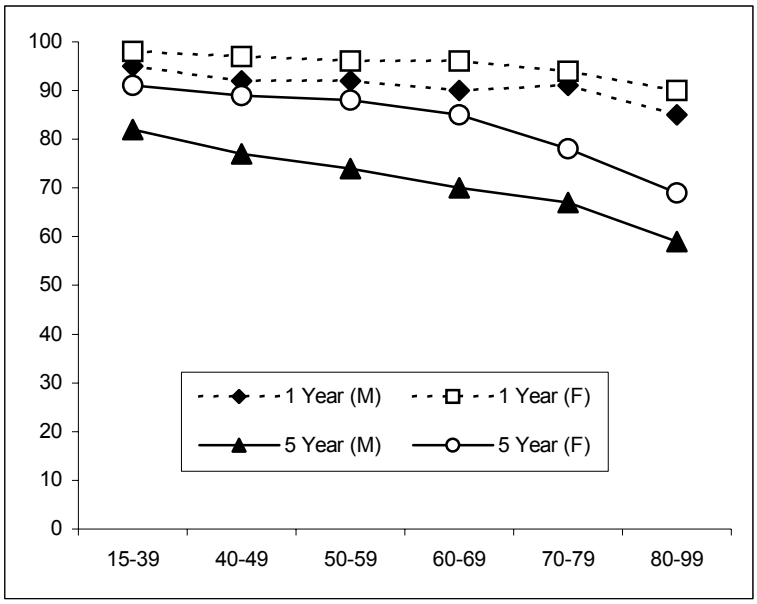



**Figure 6. Age Specific Mortality from Melanoma, England and Wales, 1981 – 2001**



## Figure 7. Survival in melanoma patients, 2001



## 1.2 Non-melanoma

Non-melanoma skin cancers are the most common cancer occurring in the UK. Although an estimated 50,000 cases were registered in 2001 across England and Wales, the under-reporting of cases masks the true figure that is agreed to be higher than that currently ascertained.

Age standardised incidence has continued to increase steadily in both sexes since the 1970s but remained higher in males during the past 30 years. By 2001, comparative rates were 65 in females and 96 in males per 100,000 population [Figure 8].

Incidence rates increase with age in males and females from age 25 years onwards. Numbers are higher in males relative to the increase in incidence; in 2001 incidence reached 1108 in males and 612 in females per 100,000 population in those aged 85 years and over [Figure 9].

The mortality rates for 2001 show that mortality from non-melanoma skin carcinoma remains low in those less than 50 years of age. Mortality in males increases steadily from age 60 years onwards peaking at 26/100,000 population in those aged 85 years or over. Female mortality rates begin to rise steeply from age 70 years and peak at 15/100,000 population in the same age group [Figure 10].

From 1970 to 2001 the age standardised mortality rates declined in both males and females. The recorded mortality halved in females (0.6 to 0.3 per 100,000 population) and nearly halved in males (1.2 to 0.7 per 100,000 population). Mortality rates recorded in 2001 are higher in males than females, having remained almost consistently double since 1970 [Figure 11].

**Figure 8. Age standardised incidence of non-melanoma, England and Wales, 1971-2001**

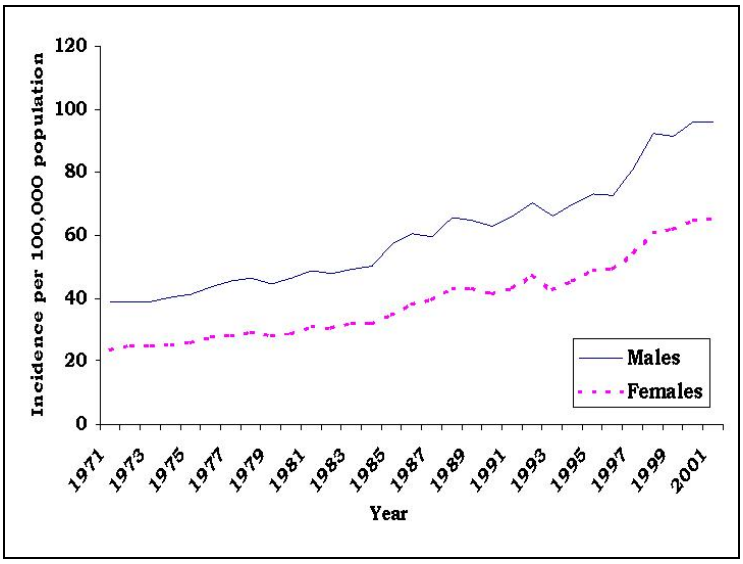



**Figure 9. Age specific incidence of non-melanoma, England and Wales, 2001**

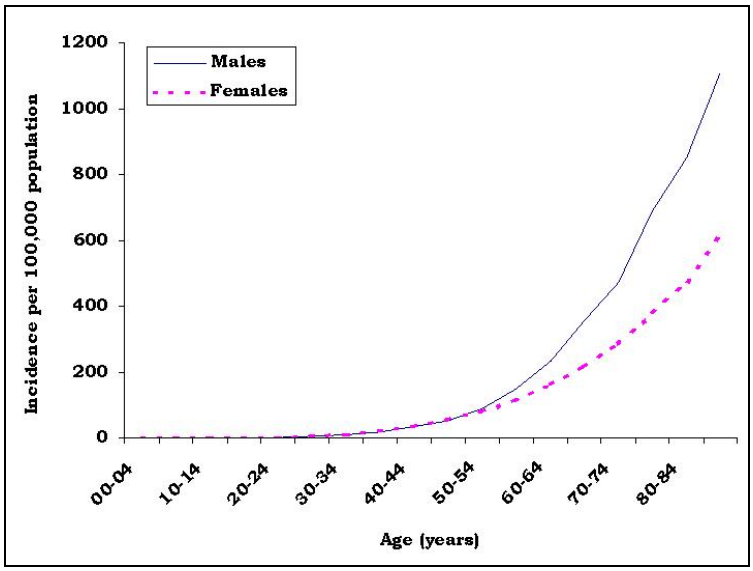


**Figure 10. Age specific mortality from non-melanoma, England and Wales, 2001**

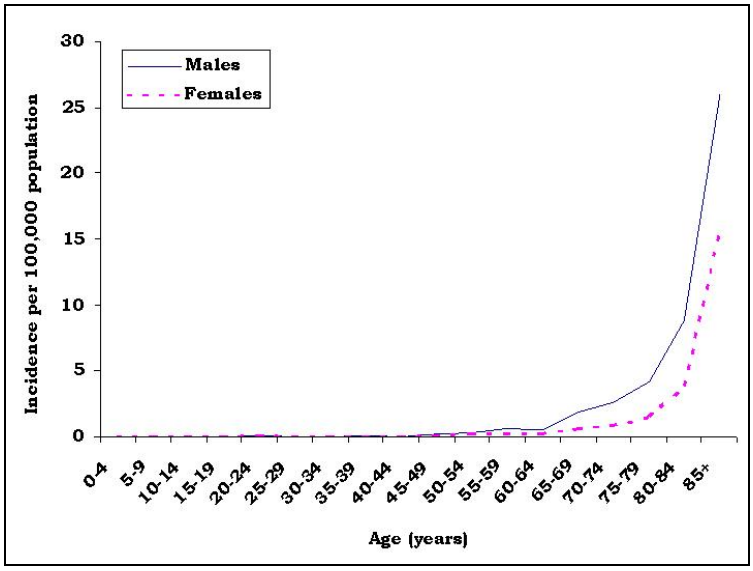
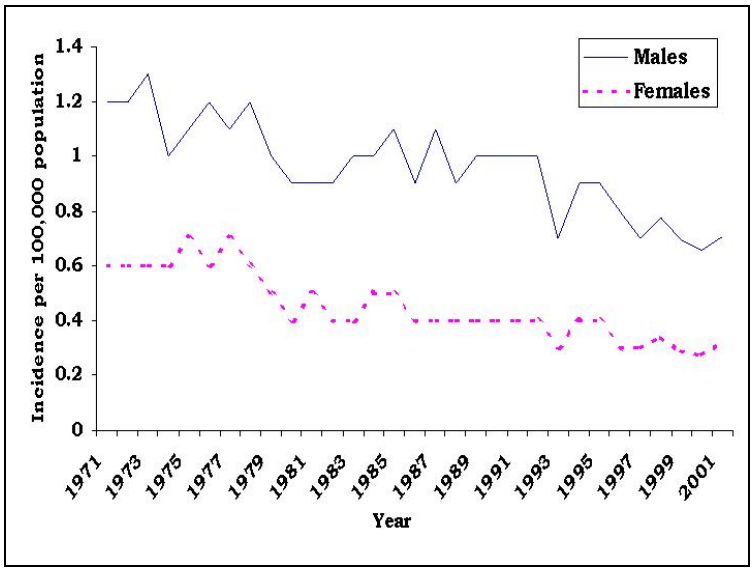



**Figure 11. Age standardised mortality from non-melanoma, England and Wales, 1971-2001**



## 2. Current service provision

The only routinely available source of data on health service usage for skin cancer collated at a national level are Hospital Episodes Statistics (HES) for England and Patient Episode Database in Wales (PEDW). These data capture in-patient admissions and day case procedures but not outpatient activity. This means they only reflect the tip of the iceberg of service provision for skin cancer patients as many are managed in primary care and of those managed in hospital most will not require a hospital admission and will be managed as outpatients. Hospitals will vary significantly according to their practices with respect to the classification of skin cancer procedures as outpatient or day case and there would also have been changes over time. These coding issues somewhat limit the usefulness of the data for local comparisons. However, as there is no other source, HES and PEDW data still give some important insights into the need of services.

Using these data a steady increase in the rate of episodes of care for melanoma and non-melanoma patients is seen in England and Wales [Figure 12 and 13]. The figures for 1997 reflect inadequate data capture processes resulting from coding changes around the time.

Examining incidence of melanoma episodes of care from 1993 to 2000, by NHS Region of Treatment, we see that almost all regions have experienced a significant increase. A greater increase in episodes of care is observed for males [Figure 14] than females [Figure 15].

Similarly, incidence of non-melanoma episodes of care from 1993 to 2000, by NHS Region of Treatment, we see that almost all regions have experienced a significant increase [Figures 16 and 17]; the exception being London, with a significant decrease in episode of care that may possibly reflect shift in activity to outpatient clinics or primary care clinics. While the pattern is similar for males and females, for non-melanoma the highest incidence is observed for the North West.

While different aspects of service provision are described using HES data in this section, readers should be aware that some of the information given might not accurately reflect the current situation. Without a nationwide audit, it is not possible to present a reliable snapshot of current services for patients with skin cancer. For example, an examination of histopathological activity for two hospital trusts revealed that only 36% of melanoma, and 41% of non-melanoma pathology data for 1995-2002 were reflected in the HES data for

the same period. HES therefore represents a gross underestimate of service utilisation by skin cancer patients.

**Figure 12. Rates of episodes of care for melanoma, England and Wales**

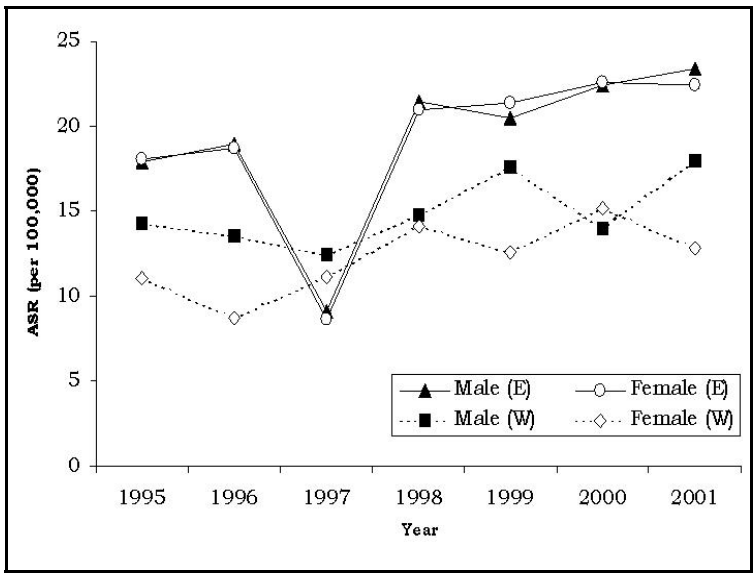



**Figure 13. Rates of episodes of care for NMSC, England and Wales**

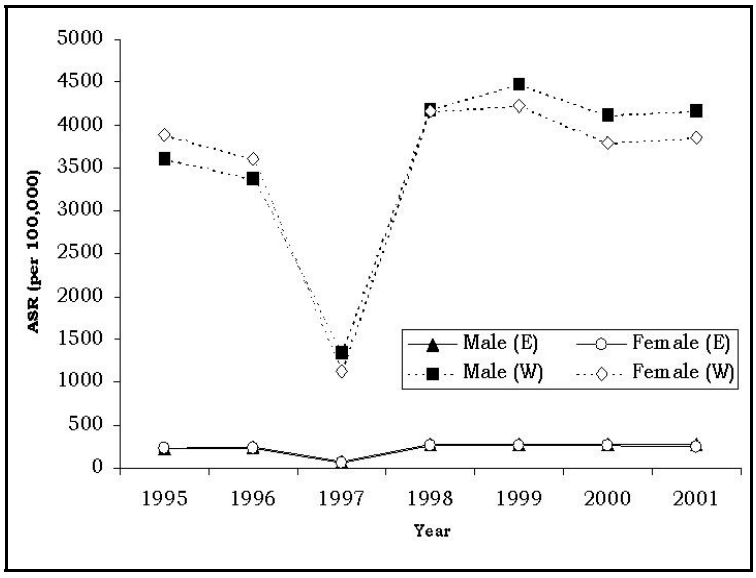


**Figure 14. Rates of episodes of care for melanoma in males, by NHS region of England, 1993 and 2000**

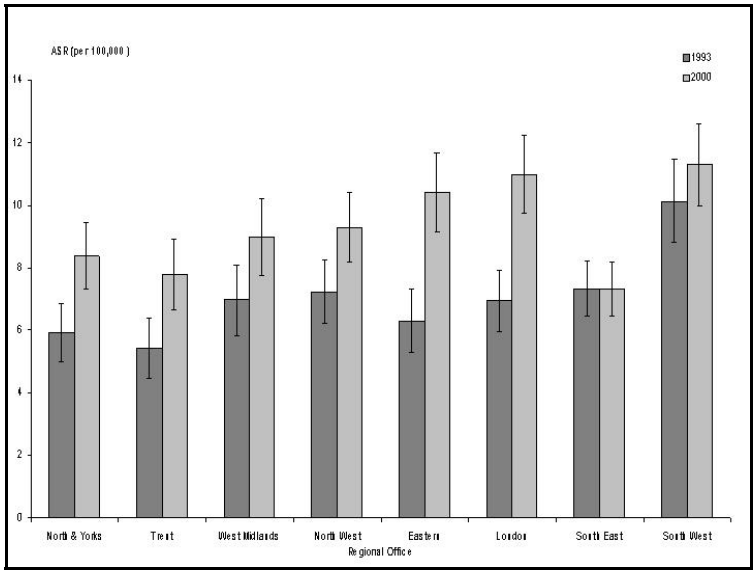



**Figure 15. Rates of episodes of care for melanoma in females, by NHS region of England, 1993 and 2000**

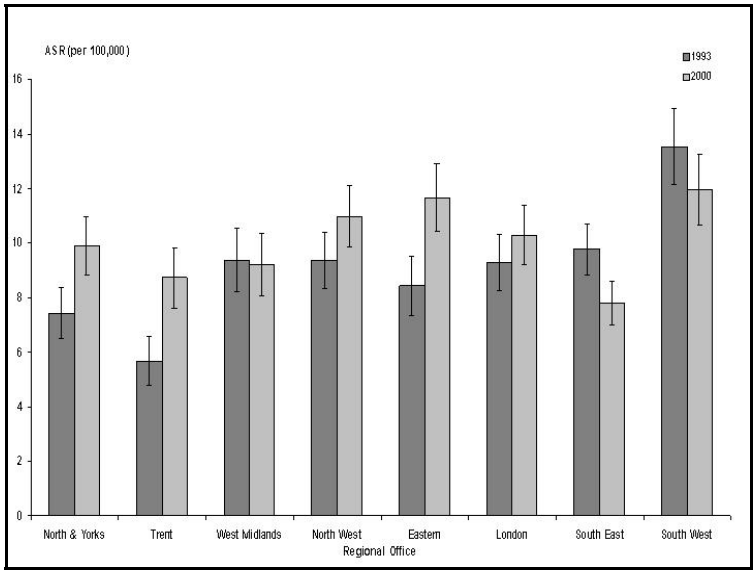


**Figure 16. Rates of episodes of care for non-melanoma in males, by NHS region of England, 1993 and 2000**

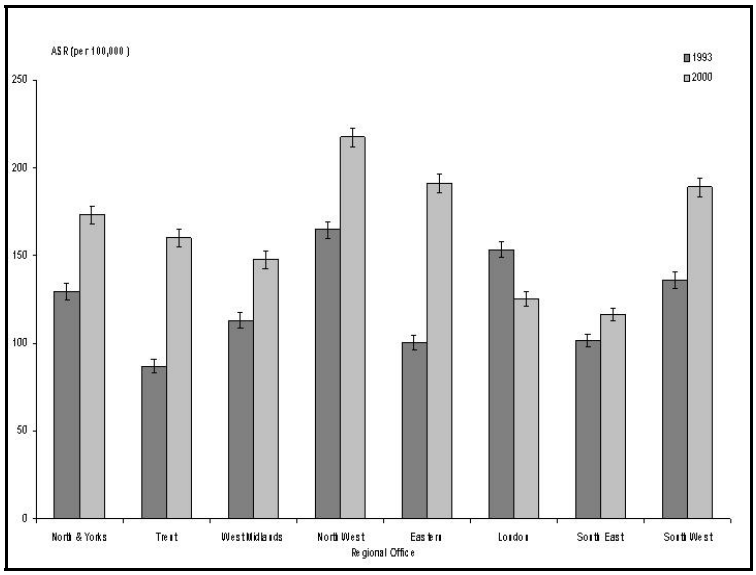
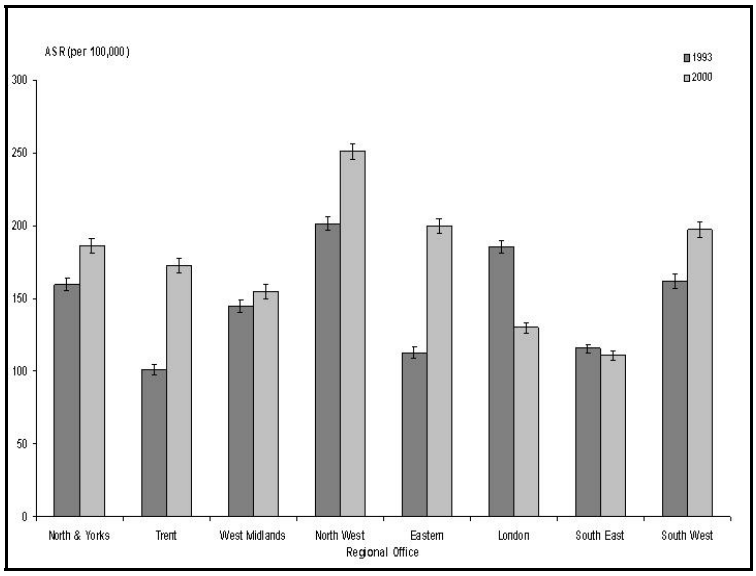



**Figure 17. Rates of episodes of care for non-melanoma in females, by NHS region of England, 1993 and 2000**



## 2.1 Clinical specialities

One of the striking characteristics of skin cancer services is the range of clinicians involved in its treatment and care, together with a variety of different patient pathways and experiences [Figure 18].

For patients with more than one episode of care, beginning in HES year 1993 or after, the proportion of patients treated by a dermatologist [Table 2] or plastic surgeon [Table 3], in their first episode has steadily increased. In contrast, treatment by general surgery [Table 4] has decreased, while for oncology [Table 5] a modest increase is observed for NMSC only.

Following a first consultation with a dermatologist, the majority of melanoma patients requiring a second consultation are seen predominantly by either dermatology or plastic surgery specialities [Table 6]. The role of general surgeons in second melanoma consultations has decreased steadily. Conversely, NMSC patients are more likely at second consultation to be seen only by a dermatologist [Table 7]. This latter observation is a suggestion of the difference in severity in disease manifestation.

**Figure 18. Number of episodes of care for malignant melanoma, by selected specialties, England 1991-2000**

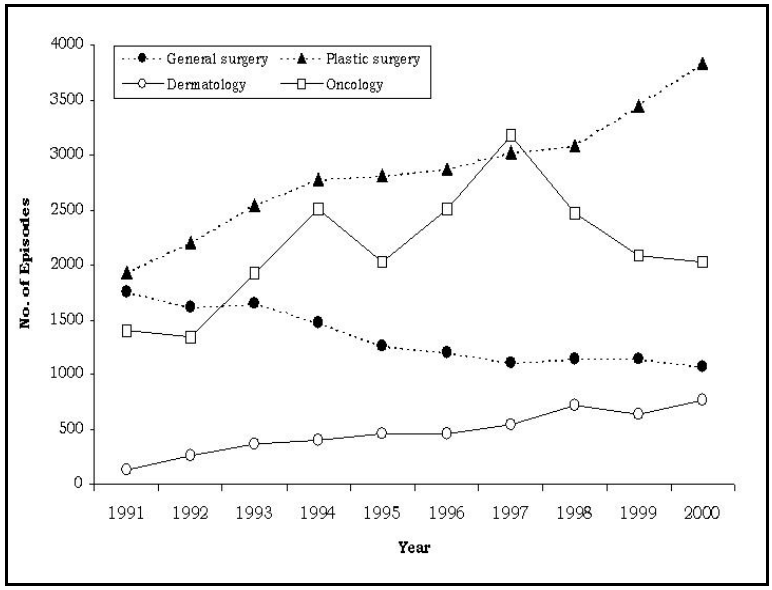


**Table 2. Proportion of patients treated by dermatologist for first episode of care**

| Year | Melanoma (%) | NMSC (%) |
|---|---|---|
| **1993** | 9.21 | 16.49 |
| **1994** | 6.77 | 22.48 |
| **1995** | 7.07 | 23.57 |
| **1996** | 6.44 | 25.47 |
| **1997** | 9.98 | 28.89 |
| **1998** | 14.70 | 31.67 |
| **1999** | 13.78 | 31.14 |
| **2000** | 16.26 | 30.37 |

**Table 3. Proportion of patients treated by plastic surgeon for first episode of care**

| Year | Melanoma (%) | NMSC (%) |
|---|---|---|
| **1993** | 41.17 | 50.65 |
| **1994** | 42.19 | 46.60 |
| **1995** | 44.91 | 44.74 |
| **1996** | 40.18 | 48.66 |
| **1997** | 44.55 | 44.27 |
| **1998** | 44.71 | 41.32 |
| **1999** | 47.91 | 41.19 |
| **2000** | 49.53 | 39.29 |

**Table 4. Proportion of patients treated by general surgeon for first episode of care**

| Year | Melanoma (%) | NMSC (%) |
|---|---|---|
| **1993** | 28.12 | 17.66 |
| **1994** | 27.36 | 16.28 |
| **1995** | 19.64 | 14.53 |
| **1996** | 21.22 | 12.16 |
| **1997** | 18.08 | 11.13 |
| **1998** | 19.65 | 9.80 |
| **1999** | 18.79 | 9.07 |
| **2000** | 13.93 | 8.96 |

**Table 5. Proportion of patients treated by oncologist for first episode of care**

| Year | Melanoma (%) | NMSC (%) |
|---|---|---|
| **1993** | 12.76 | 2.80 |
| **1994** | 14.73 | 2.17 |
| **1995** | 19.04 | 2.74 |
| **1996** | 23.04 | 1.53 |
| **1997** | 18.61 | 3.25 |
| **1998** | 13.71 | 3.23 |
| **1999** | 11.40 | 3.79 |
| **2000** | 11.78 | 3.42 |

**Table 6. Clinical specialty at second consultation for melanoma patients treated by dermatologist at first episode of care**

| Year | Dermatology (%) | Plastic Surgery (%) | General Surgery (%) | Oncology (%) |
|---|---|---|---|---|
| **1993** | 44.79 | 40.63 | 10.42 | 1.04 |
| **1994** | 36.76 | 41.18 | 19.12 | 0.00 |
| **1995** | 35.59 | 47.46 | 13.56 | 1.69 |
| **1996** | 39.62 | 34.91 | 16.04 | 5.66 |
| **1997** | 37.88 | 43.94 | 11.36 | 2.27 |
| **1998** | 40.93 | 44.56 | 7.77 | 1.55 |
| **1999** | 36.31 | 54.76 | 6.55 | 0.60 |
| **2000** | 40.80 | 46.55 | 6.32 | 1.72 |

**Table 7. Clinical specialty at second consultation for NMSC patients treated by dermatologist at first episode of care**

| Year | Dermatology (%) | Plastic Surgery (%) | General Surgery (%) | Oncology (%) |
|---|---|---|---|---|
| **1993** | 75.39 | 14.51 | 4.02 | 1.37 |
| **1994** | 77.38 | 13.83 | 3.68 | 0.56 |
| **1995** | 73.40 | 16.81 | 4.59 | 0.48 |
| **1996** | 77.55 | 12.60 | 3.13 | 1.16 |
| **1997** | 76.40 | 13.47 | 2.56 | 1.64 |
| **1998** | 75.05 | 14.29 | 2.53 | 1.79 |
| **1999** | 68.73 | 17.05 | 1.85 | 2.24 |
| **2000** | 63.75 | 20.86 | 2.45 | 2.83 |

## 2.2 Cosmetic camouflage services

Cosmetic camouflage (CC) services for skin cancer patients in England and Wales was examined by means of a questionnaire survey to all 37 network leads for skin cancer. The survey was designed and conducted by the NCC-C in consultation with members of the GDG to examine issues around patient management and service provision.

A seventy-percent response was achieved with all respondents indicating having a CC service in their network. The existence of such a service varied from less than 2 years to greater than 20 years in some networks. A total of 40 such service locations were identified across the 30 networks responding. The Red Cross provided the vast majority of these CC services.

Although 87% of respondents felt there was adequate provision of service in their network, none of the networks had a specific referral criteria. Examination of factors affecting the decision to refer a skin cancer patient [Table 8] highlighted concordance (>80%) in patient management on issues related to age, gender, and interference of appearance with work, social or personal relationships.

**The consensus of views among respondents suggested that the demand for CC services arises more frequently for other skin conditions rather than skin cancers.**

**Table 8. Factors affecting patient management decisions in referral for cosmetic camouflage**

| Factor | Decision is strengthened (%) | Decision is not affected (%) | Decision is weakened (%) |
|---|---|---|---|
| Age > 70 years | 0 | 92 | 8 |
| Age < 50 years | 0 | 85 | 15 |
| Male gender | 0 | 92 | 8 |
| Female gender | 12 | 88 | 0 |
| Location of anatomical site | 64 | 36 | 0 |
| Appearance interferes with employment / studying | 92 | 8 | 0 |
| Appearance interferes with leisure activities | 77 | 23 | 0 |
| Appearance interferes with shopping | 50 | 50 | 0 |
| Appearance interferes with household chores | 38 | 62 | 0 |
| Appearance interferes with social activities | 88 | 12 | 0 |
| Appearance interferes with intimacy in relationships | 87 | 13 | 0 |
| Patient has had a difficult treatment history | 28 | 72 | 0 |
| Patient has unrealistic expectations of outcome | 31 | 50 | 19 |
| Patient requests referral | 67 | 33 | 0 |
| Accessibility of service | 48 | 52 | 0 |

# Appendix B

# The skin cancer patient experience – a report for the NICE skin tumours service guidance.

Department of Social Medicine

University of Bristol

## Commissioned by the skin tumours GDG and the National Collaborating Centre for Cancer

# 1. The skin cancer patient experience

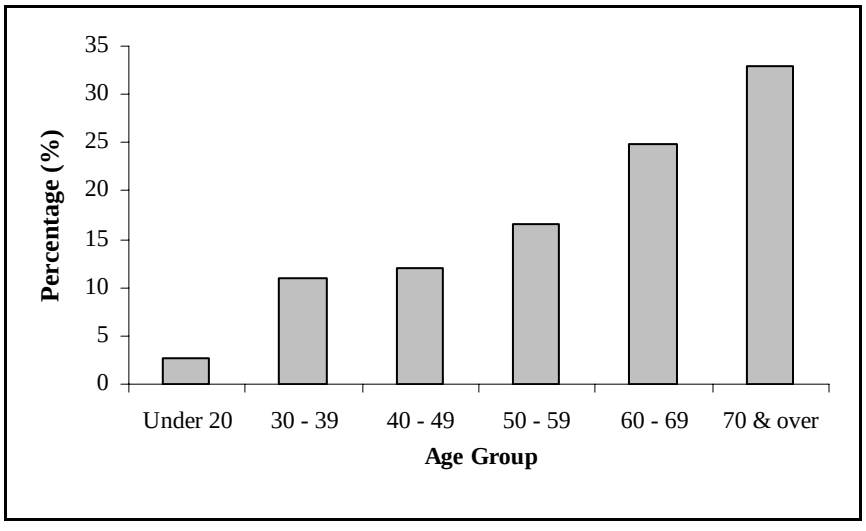
The needs of skin cancer patients in relation to current service provision were investigated by the means of a qualitative survey. The survey was designed by the NICE Patient Information Unit in consultation with members of the skin tumours GDG and NCC-C to examine issues along the skin cancer patient pathway.

A successful application for ethics committee approval for the study was coordinated by Dr Julia Verne and members of the NCC-C. Distribution of the questionnaire and agreement with local Trust research committees was coordinated by Dr Andrew Morton (NCC-C) and Barbara Moore (Velindre NHS Trust). All collected data was analysed by qualitative researchers from the Department of Social Medicine, University of Bristol.

## 1.1 Respondents' characteristics

Of the 111 patients who completed the questionnaire there was a slightly higher response rate from women: 56% of respondents were female, 41% were male and data were not provided for 3%. The age distribution of respondents [Figure 1] reflects the incidence of skin cancer with 58% of all respondents aged 60 or over, 28% aged between 40 and 60 and only 14% aged under 40.

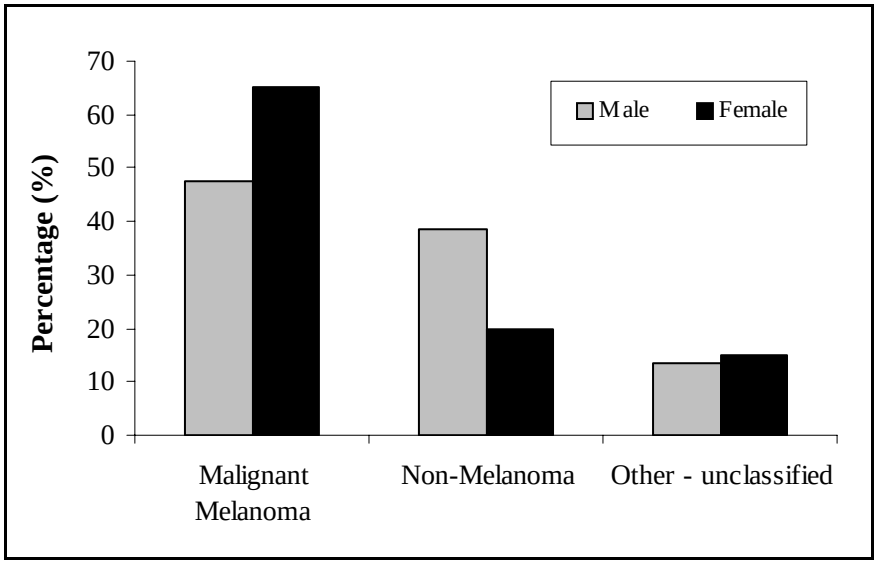
**Figure 1. Age distribution of skin cancer questionnaire respondents**



## 1.2 Skin cancer type

Fifty-four percent of respondents had malignant melanoma, 26% had non-melanoma and 30% had either other, unclassified forms of skin cancer or the data were missing. When analysed according to gender [Figure 2], the proportion of female respondents who had malignant melanoma was higher than the proportion of male sufferers: 63% of women compared with 46% of men had malignant melanoma whilst 37% of men reported having a non-melanoma compared with 19% of women. Non-melanomas were less common in the under 60s, only 21% of respondents, whereas the frequency of malignant melanoma was more normally distributed ranging from age 30 to over 70.

**Figure 2. Distribution of skin cancer type by gender of respondents**




## 1.3 Problems with diagnosis

Over forty percent of respondents sought advice from someone other than their doctor, in most cases from their partner, family or friends, before their cancer was diagnosed. Speed of diagnosis and treatment appeared to be important for reducing patients' stress. During the time period from when respondents first thought something was wrong to diagnosis, a third were worried, either that it might be something serious like cancer (34%) or because there seemed a long waiting time for diagnosis and treatment (16%) or because their GP had not recognized it or had been slow to refer (20%). The main reason why 60% of respondents did not worry was due to the prompt treatment.

Of the 35 respondents who considered there had been a delay in obtaining a diagnosis, 25% attributed it to problems with their GP's lack of knowledge or incompetence, whilst 25% identified problems with the hospital in terms of pressure on the appointment system and staff shortages. Such patients felt angry, disappointed and shocked, although others were more philosophical and resigned to the delay.

## 1.4 Diagnostic tests and treatment

Only 12% of respondents had their cancer identified and treated by their GP and almost all were happy with the treatment. Most patients were referred to hospital for tests and treatment (78.3%) and reported a favourable experience: 18% found the service prompt and efficient, 14% said the staff were very competent and caring, and 14% reported that the service was excellent. Only 9% made negative comments about their experience and these were linked to waiting times and worry about the delay and limited information provided about their type of skin cancer. For 11% of respondents their skin cancer was found by someone other than a hospital doctor or their GP; in most cases either they or their partner first noticed it.

Treatments given for skin cancer were most commonly: surgery (45%); excision (39%); chemotherapy or radiotherapy (10%); skin graft (8%); biopsy (7%) and interferon (5%). Respondents reported seeing both doctors (65%) and nurses (63%) during their treatment and some were specific, identifying their consultant (31%), their GP (13%), a plastic surgeon (11%), a dermatologist (8%), an oncologist (5%) and a radiologist (5%). Only 8% thought they should have seen other healthcare professionals such as a counsellor, dietician or a clinical nurse specialist.

48.6% of respondents were not offered advice about special make-up to help them hide their scars but only 17% would have liked such advice; for the others the scar was either too small or not easily visible. Only 13% of respondents considered they had special needs during their treatment, 40% requiring emotional support; 72% reported that their special needs had been met.

## 1.5 Information requirements

When first told they had skin cancer respondents most wanted to know how serious it was (40%) and about their treatment, when they would have it, whether it was painful and

necessary, and whether it would be successful (52%). The other most important issues were whether the cancer had spread (20%) and whether it would reoccur (13%).

## 1.6 Patient support

Following diagnosis 40% of respondents were able to talk to their partner, family or friends about their worries. Support was also available from clinicians with 24% discussing their worries with a nurse, 21% with their consultant, 17% with a hospital doctor and 7% with their GP. Only 4% had no one to talk to. Fourteen percent of respondents would have liked to have been able to talk to someone else, 25% of these to a clinical nurse specialist.

A majority of patients felt their healthcare professionals gave them enough time to discuss their concerns (69.3%) compared with only 8% who felt they definitely were not given enough time. Most reported that they were given just about the right amount of information (85%) and that they understood everything they were told (75%). Only 10% would have liked more information. Three quarter of respondents were given printed information, in the form of booklets and leaflets, but only a quarter of them received materials about their own cancer to take away with them.

Despite the above, 25% of respondents still felt that there were other times that they would have liked more information, mainly about their treatment and possible side effects, or about possible recurrence in the future.

Half of respondents (54%) were invited to bring a relative or friend to an appointment for support but of the remainder, some knew they could bring a family member whilst others were asked that their family got checked for cancer rather than accompanying them to the consultation.

## 1.7 Access

Most respondents reported little difficulty in accessing services for their skin cancer. Of the 10% who experienced difficulties, problems included: waiting list times; access to information; parking at the hospital; and one respondent had their notes lost.

## 1.8 Preferred health professional

Having continuity of care and seeing a health professional who is well informed are the two key concerns for patients when seeing clinicians. When visiting the clinic 40% of

respondents prefer to see the consultant because they are well informed, give patients confidence, their examination is thorough, and most importantly they provide continuity of care. Approximately a quarter preferred to see a doctor (unspecified), for essentially similar reasons, to ensure continuity of care and because they are well informed. Twenty-three percent prefer to see a nurse because they are well informed and approachable. Only 10% of respondents had no particular preference as to who they saw in clinic.

At the time of completing the questionnaire, 72% were being followed-up and of these the majority were seeing a hospital doctor (92%). The length of follow-up ranged from one month to seven years.

## 1.9 Self-examination

Sixty percent of respondents were happy to check themselves for skin cancer, although they would still want regular check-ups and they would need good instructions. Twenty percent had concerns about checking themselves i.e. these patients were worried that they might miss something suspicious, that they could not examine parts of their body, and that they would prefer a professional to check them. Patients with melanoma were more likely to have concerns about self-checking due to fears that they might miss something.

## 1.10 The effect on patients lives

Two thirds of respondents reported that skin cancer had affected their life, again this was more frequent amongst patients with melanoma. The most common effects were an increased awareness of the dangers of the sun (30%), the physical impact (11%), and a decision to enjoy life (10%). Some respondents reported negative emotions feeling depressed, bitter, anxious and worried (21%), particularly about finding more moles. Others think more about their health and no longer take it for granted.

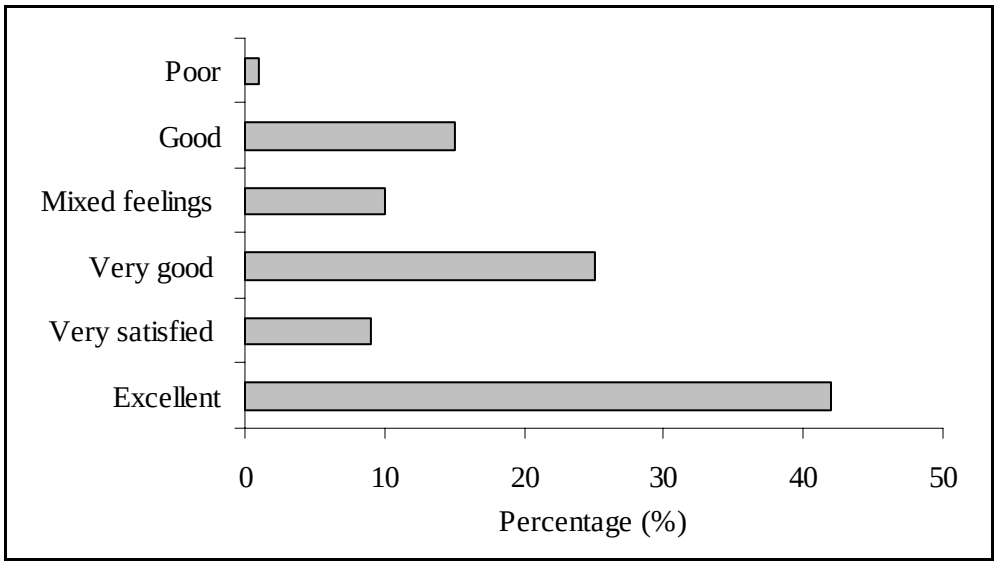
## 1.11 Health professionals respect for patients

Most respondents considered that health professionals respected what they said (84%), whereas 4% had mixed views about this and 5% said they did not show respect. Negative views related to professionals being too busy, patients not being treated as individuals, and their views not being taken seriously.

## 1.12 Satisfaction with treatment

The majority of respondents considered their overall treatment [Figure 3] to be either very good (24%), excellent (41%) or were very satisfied (9%). Nine percent had mixed feelings due to poor primary care but good hospital services or problems in diagnosis. One respondent who judged their treatment to be poor compared it with New Zealand where they felt the treatment was excellent because they take cancer seriously.

**Figure 3. Patient satisfaction with treatment**




## 1.13 Potential for service improvement

Twenty-seven percent of respondents did not think services could be improved compared with 49% who suggested possible improvements. Key improvements included shorter waiting times (28%); concise, clear and easily accessible information leaflets (20%); more advice on the dangers of the sun (11%); and greater GP education about skin cancer (4%).

## 1.14 Conclusion

The majority of respondents, irrespective of gender, age and type of skin cancer, were very satisfied with the care they had received, in terms of access to services, speed of diagnosis, treatment, information and support. Negative experiences related to delays in diagnosis, referral and treatment that were attributed partly to lack of primary care knowledge, and partly to insufficient hospital capacity. Key concerns for patients were continuity of care, being treated by a well-informed clinician, access to information, and prompt diagnosis and treatment.

# Appendix C

# Literature search strategy

In order to identify evidence relevant to the research questions set by the GDG, literature searches were undertaken of electronic databases of published studies. The following databases were accessed via the Health of Wales Information Service (HOWIS) e-Library:

- Medline
- Embase
- EBM Reviews/Cochrane Library
- Cinahl
- BNI
- Psychinfo
- AMED
- HMIC
- ASSIA for Health

Search strategies relevant to the research questions were constructed by the Information Specialist, to ensure high sensitivity and hence optimise the number of studies identified.

Each search strategy was constructed according to its specific population, intervention, comparison and outcome and the syntax used was adapted to each database searched. For example, the following set of syntax was used in all search strategies which sought to identify studies of patients with skin cancer via the Medline database:

1. exp Skin Neoplasms/
2. exp "Neoplasms, Adnexal and Skin Appendage"/
3. exp Melanoma/
4. exp Carcinoma, Squamous Cell/
5. exp Carcinoma, Basal Cell/
6. exp Carcinoma, Merkel Cell/
7. exp Lymphoma, T-Cell, Cutaneous/
8. sarcoma, Kaposi/

9. exp Nevus, Pigmented/
10. (Basal adj2 carcinoma$).tw.
11. (basal adj1 cancer$).tw.
12. (basal adj1 neoplas$).tw.
13. (basal adj1 tumo?r$).tw.
14. (basal adj1 epithelioma$).tw.
15. (basal adj1 malignan$).tw.
16. basalioma$.tw.
17. (basocellular$ adj carcinoma$).tw.
18. BCC.tw.
19. (basosquamous adj1 carcinoma$).tw.
20. (squamous adj2 carcinoma$).tw.
21. (squamous adj1 tumo?r$).tw.
22. (squamous adj1 cancer$).tw.
23. (squamous adj1 neoplas$).tw.
24. (squamous adj1 epithelioma$).tw.
25. (squamous adj1 malignan$).tw.
26. SCC.tw.
27. (merkel adj2 carcinoma$).tw.
28. (merkel adj1 cancer$).tw.
29. (merkel adj1 tumo?r$).tw.
30. (merkel adj1 neoplas$).tw.
31. (merkel adj1 malignan$).tw.
32. MCC.tw.
33. (t adj1 lymphoma$).tw.
34. (cutaneous adj1 lymphoma$).tw.
35. (mycos$ adj fungoid$).tw.
36. sezary$.tw.
37. (kaposi$ adj sarcoma$).tw.
38. melanoma$.tw.
39. (maligna$ adj2 lentigo).tw.
40. LMM$1.tw.
41. nonmelanoma$.tw.
42. NMSC.tw.
43. dermatofibrosarcoma$.tw.
44. (apocrine adj carcinoma$).tw.
45. (sweat adj1 carcinoma$).tw.
46. (sweat adj1 tumo?r$).tw.
47. (sweat adj1 neoplas$).tw.
48. (sweat adj1 cancer$).tw.
49. (sebaceous adj carcinoma$).tw.
50. (sebaceous adj tumo?r$).tw.
51. (sebaceous adj neoplas$).tw.
52. (sebaceous adj cancer$).tw.
53. (eccrine adj (poroma$ or porocarcinoma$)).tw.
54. (eccrine adj epithelioma$).tw.
55. SSDC.tw.
56. Basal Cell Nevus Syndrome/
57. ((naevoid or nevoid) adj3 syndrome$).tw.
58. gorlin$.tw.
59. (malignant adj1 (nev$ or naev$)).tw.

60. ((skin or derm$ or cutaneous or epithelial or epidermoid$) adj1 (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$)).tw.
61. or/1-60

The Information Specialist sifted the initial list of records generated by each search for relevance to the topic area. The Researcher made the final study selections.

There was a wide range of topic areas addressed by the clinical questions and for some questions, a very large volume of potential studies identified by the literature searches. For these questions with a large list of records, the search strategies were re-run with the addition of syntax filters to identify only RCTs and systematic reviews.

Citations and where available, abstracts of studies sifted as relevant were imported to Reference Manager Version 11 databases, one for each research question, or set of related questions. The Researcher reviewed the sifted list of studies in each database and further reduced the list to studies to be ordered for critical appraisal and possible inclusion in the evidence review. Only studies published in English were critically appraised.

Research questions were set by the GDG at meetings which took place over a period of 13 months. Subsequently the literature searches were undertaken over a similar time period and in order to ensure that recently published studies were considered for inclusion, searches were re-run up to the end of January 2005. Studies that appear in the evidence review with a publication date later than January 2005 were identified either by GDG members or as a result of stakeholder consultation.

# Appendix D

# Data submitted by registered stakeholders

During the first consultation period in the development of this guidance, a number of registered stakeholders from nine NHS Trusts in England provided audit data on current primary care activity with regard to skin cancer. The data provided evidence of the proportion of skin tumours that are currently managed in primary and secondary care, and is tabulated below. This data demonstrated that the proportion of skin cancer tumours managed in primary care had range 1.2% to 17%. The audits found that between 1.4% and 13% of melanoma tumours are managed in primary care. This proportion for SCC had range 0.7% and 10% and for BCC had range 1.3% to 8.8%.

## Stakeholder responses to first consultation: Submitted proportions of skin malignancies managed in primary and secondary care

| Stakeholder | Proportions of skin lesions treated in primary care and secondary care (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Primary care | | | | | Secondary care | | | | |
| | Skin cancer | Melanoma | SCC | BCC | Rare malignancies | Skin cancer | Melanoma | SCC | BCC | Rare malignancies |
| Dr A D Ormerod on behalf of British Association of Dermatologists | 4 | | | | | 96 | | | | |
| British Association of Dermatologists - Derbyshire Royal Infirmary | | | | 8 | | | | | 92 | |
| British Society for Dermatology Surgery - Newcastle | 1.2 | 1.4 | 0.7 | 1.3 | 0 | 98.8 | 98.6 | 98.6 | 98.3 | 100 |
| Cancer Services Collaborative 'Improvement Partnership' (CSCIP) Derby | | 13 | 10 | 8 | | | 87 | 90 | 92 | |
| Nottingham Cancer Centre | | | | 8.3 | | | | | 91.7 | |
| Nottingham Cancer Centre | | | | 8.3 | | | | | 91.7 | |
| Sheffield skin cancer MDT | | | | <4 | | | | | >96 | |
| National Cancer Network Clinical Directors' Group - Brighton | 17 | | | | | 83 | | | | |
| British Society for Dermatology Surgery | 1.2 | | | | | 98.8 | | | | |
| **Range** | 1.2-17 | 1.4-13 | 0.7-10 | 1.3-8.8 | Single value | 83-98.8 | 87-98.6 | 90-98.6 | 91.7-98.3 | Single value |

# Appendix E

# Living with Skin Cancer

# A reflection on NHS services

# A paper from James Partridge

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**Registered Charity 1011222**

## Living with skin cancer – a reflection on NHS services

The incidence of skin cancers is on the increase. They affect people from all communities and age groups, although predominantly in the over 50 age range. People with skin cancers receive a plethora of diagnostic and treatment services from the NHS very much dependent on the medical/surgical specialty to which they are referred, usually, by their GP. This paper has been written by Changing Faces in an attempt to review the quality of those services and point up some of the problems as experienced by patients and their families.

It has not been possible for this paper to survey the views of many patients but reference is made to two psycho-social audit studies (1999, 2000) conducted by the Centre for Appearance and Disfigurement Research at the University of the West of England and to the recent All Party Parliamentary Group on Skin's report. It is believed that some of the problems and concerns of patients have been authentically reflected.

## Skin cancer from a patient's perspective

The three major types of skin cancer are the highly curable basal cell and squamous cell carcinomas and the more serious malignant melanomas. Death rates from basal and squamous cell carcinomas are low. Although basal cell and squamous cell carcinomas do not usually spread to other areas of the body, they can cause significant damage and disfigurement if left untreated. Exposure to the sun's ultraviolet rays is the most important factor in the development of skin cancers. Preventative measures to avoid sun exposure can reduce this risk. Personal/family history of skin cancer is an additional risk factor.

The first indication that a patient has that they may have a skin cancer is the appearance of a sore, mole or skin pigment change. Their decision as to when to seek an examination by a medical practitioner will be influenced by their family and life circumstances but, given that early diagnosis is highly desirable, the first contact with their GP will indicate how serious the problem may be. Some patients present very late with a large and difficult wound.

Lay knowledge about skin cancer is rising as health education programmes attempt to get preventative messages to the public. But much less is known about what happens if you do have a diagnosis from your GP that you may have a skin cancer. Some GPs carry information leaflets but many patients are left without written information, being referred to a dermatologist, sometimes weeks or months ahead. If they have access to the Internet, they may be to obtain additional information. Today, there is a mass of information available, including from NHS Direct, CancerBacup and other charities.

Skin cancers most commonly arise in the sun-exposed areas of the body. Basal cell carcinomas often occur on the face, head and neck where their surface appearance varies from a change in skin pigmentation to a moderately visible sore that crusts, oozes or bleeds regularly. The carcinoma may be much larger than the patient expects based on the size of the skin lesion visible to the naked eye.

Treatments for skin cancer include curettage with or without electrodessication, excision, cryosurgery, topical chemotherapy and radiotherapy, as well as Mohs micrographic surgery (MMS). It is difficult for the medical staff or the patient to predict how much tissue will be removed during surgery, and hence the resulting degree of disfigurement.

Some of the reconstructive procedures following excision are carried out immediately by a dermatologist or by a plastic surgeon. Some patients are left with significant disfiguration and, after MMS especially, can have highly visible and permanent facial scarring. Other patients may have a scar that is barely noticeable.

**Access to NHS services**

Patients who are referred by their GP for further investigations about a possible skin cancer are usually referred to a dermatologist but, depending on local circumstances and especially if the skin lesion is already large, the referral may be to a plastic surgeon. Once the initial biopsy has been completed, subsequent treatment may be done solely by a dermatologist or by a team involving a plastic surgeon (and others). Concern has been

expressed that the pathway of care to be taken by patients is not as clear as it could be, and that GPs could better explain to patients what to expect.

The speed of the referral is also often a concern to patients. They may not be informed that the type of skin cancer suspected by the GP will determine how urgent is the referral – if a melanoma, immediate two-week referral, whereas if a basal cell carcinoma a longer wait may be involved.

There are believed to be regional and local variations in NHS tertiary dermatology and plastic surgery services but Changing Faces has not been able to unearth any authoritative statistics to describe this. Patients report differential access times but it is not known whether this is due to differential diagnoses.

Patients expect to have some choice about the hospital and specialist they are referred to but in the absence of publicly available and meaningful data on the performance of different clinics, this choice is largely uninformed – and patients thus have to rely on their GP's knowledge and practice. Analysing websites such as Dr Foster does provide some general figures but more cancer-specific data is required and it is always difficult to know how reliable the figures are.

**Managing the psychological and social effects of skin cancer**

Skin cancer can be the cause of major psychological and social distress which can be expressed before a definite diagnosis and be manifested for many weeks and months afterwards, sometimes lasting for the rest of a patient's life. Studies and surveys suggest that patients receive a very variable experience in NHS primary and tertiary care settings but that the overall sense is that information and support is inadequate.

In best practice, the diagnosis of skin cancer should be accompanied by clear information about its cause, effects and subsequent treatment and with support for the patient and family. Surveys show that patients often have very little understanding of the cause and effects of their skin cancer and are not aware of the different types of treatments that are available. In particular, they

are not well prepared for the change in appearance brought about by surgery nor are they supported effectively in dealing with this change once back at home or in the community. Given that much treatment is now done on a day surgery basis, the lack of contact and relationship with hospital staff compounds – or perhaps explains – this situation. Furthermore, the uncertainty about the outcomes of treatment can leave some patients in a state of anxiety for long periods afterwards.

The majority of problems experienced by people with a visible disfigurement after skin cancer are psycho-social rather than medical in nature. Typical difficulties reported are:

- embarrassment due to bleeding, dressings etc
- reactions to the disfigurement from the general public such as staring, comments and questions about the cause
- low self-confidence and restricted social life
- anxiety due to waiting for hospital appointments or biopsy results
- fear of recurrence
- problems with caring for the surgical wound at home
- fear about the local anaesthetics
- worries about the appearance of the scar
- issues of guilt and stigma arising from diagnosis of a preventable cancer
- anxiety due to a cancer diagnosis
- fear of increased susceptibility to cancers in general (sometimes related to earlier treatment for other cancer).

People with skin cancers can therefore experience serious difficulties in social situations, high levels of social anxiety and depression, lowered self-esteem and self-confidence and problems in getting (back to) employment.

Treatments for skin cancer do not usually result in severe disfigurement (MMS is an exception) but, importantly, research shows that the severity of a disfigurement is not positively correlated with the distress it causes (see Lansdown et al, 1997). What may be perceived by others as relatively ‘minor’ disfigurements can cause considerable problems especially if they appear in the “communications triangle” on the face (between the corners of the eyes and the chin), which is where attention is focused in social interactions.

Research shows that levels of adjustment are not predicted by the physical and functional characteristics of a disfigurement (e.g. severity, location) but by psycho-social factors such as:

(a) having realistic information about the treatment options available

(b) getting quality support from family, friends, an appropriate professional or agency

(c) learning how to manage other people’s reactions in social situations of all kinds.

However, current care provision is not yet designed to promote these factors. Current care provision within the NHS is based primarily on the biomedical model, with medical and surgical interventions offered to address appearance-related concerns. For the majority of patients, therefore, their psycho-social needs remain unassessed and unaddressed. The impact of these problems is variable, but for many they may lead to social withdrawal and a reluctance to participate in the activities of everyday life.

**Social support and coping**

In the absence of a comprehensive service to assess and address psycho-social need in clinic settings, many patients have to rely on family and friends around them for support. Some family members or friends may feel

overwhelmed by this – certainly in the study of the emotional needs of the Mohs patients, much more input from clinic staff in the form of information and support was clearly needed for these significant others, in order to enable them to provide the necessary support.

Coping research shows that some individuals cope apparently successfully with their disfigurement while others remain psychologically, functionally and socially very vulnerable. People adopt a variety of coping strategies: avoidant strategies include those of a behavioural nature (e.g. avoiding social situations, escapism in drink, drugs etc), distraction techniques (ignoring the problem by immersing oneself in another activity) and cognitive avoidance strategies such as denial and distancing - “I try and not let it get to me”. Non-avoidant strategies include, cognitively, positive self-talk (“I’m different but I am as good as everyone else”) and social comparison (“I’m lucky - I could have been burned”). Pro-active behavioural strategies, involving taking the initiative in social situations, are also used and can be learned and developed. Talking to a partner, family member or friend about problems experienced or emotions can also be effective forms of coping.

It would seem that it is not the actual strategies that people use that count but the number of strategies they perceive are available to them. The key seems to be the ability and flexibility to use different strategies in different situations (Robinson 1997 as cited in Lansdown et al).

In other fields of cancer treatment (e.g. Head and Neck Cancer), relevant health professionals such as Clinical Nurse Specialists, have acquired training in the psycho-social needs of their patients and have thereby devised programmes and services to facilitate these coping strategies and supports (Clarke 2002).

**Professional resources and training**

The number of patients presenting with skin cancer is growing sharply each year and it is important that the NHS professionals responsible for their care have a specialised and well-informed knowledge about their bio-psycho-social concerns and how best to address them. At primary and tertiary levels, there

is a need to increase awareness of the psycho-social effects of skin cancer and to design services accordingly – especially in order to provide patients with clear and easily understood information and with support for living with their visible difference.

Training of dermatology specialists, especially nurses, and of GPs and their staff is strongly indicated by surveys of needs and other research work.

**Self-help resources and support groups**

There are a few skin cancer-specific support groups and research foundations but they are mostly North American. CancerBacup and Macmillan are the primary sources of information in the UK.

Changing Faces has produced a range of self-help guides that are relevant for patients with skin cancer. These are mostly acquired by individuals though some health professionals/clinics buy them in bulk to give out to their patients. Titles include:

- Everybody's staring at me! How to communicate when you have an unusual face
- Meeting new people, making new friends: A step-by-step guide for people with a facial disfigurement
- What happened to your eye? Understanding and managing disfigurement around the eye
- When a medical skin condition affects the way you look: A guide to managing living with an unusual appearance
- When cancer affects the way you look: Managing the change in your appearance
- When facial paralysis affects the way you look: Managing the change in your appearance

- Talking to health professionals about disfigurement: A step-by-step guide for people with a facial disfigurement.

**Recommendations**

The existence of the NICE Skin Cancer Guidelines Group is welcomed and it is hoped that it will be able to use these observations, although they are informed by limited evidence and limited user consultation.

**The primary concerns are:**

- how patients receive information about their condition and the referral process
- how the pathway of their care is developed and explained to them and their families
- how support is provided out of the hospital context
- how their psycho-social needs are assessed and addressed
- how health professionals are trained about the psycho-social as well as clinical aspects of care.

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Changing Faces

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# Appendix F

# NICE Service Guidance

# The Skin Tumours Guideline Development Group (GDG)

# Management of in-transit metastatic melanoma

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# Management of in-transit metastatic melanoma

In-transit metastases are cutaneous or subcutaneous deposits of melanoma which develop between the site of primary disease and the regional lymph nodes. This pattern of disease has also been caused satellitosis and non-nodal regional recurrence. Local recurrences should also be considered in the same prognostic category unless the recurrence is contiguous with an excision scar or graft and bears an in-situ component [(1)]. The prognosis of true local recurrence defined in this way is much better than is associated with in-transit disease and implies inadequate treatment of the primary melanoma.

In-transit metastases result from lymphatic dissemination of melanoma cells to skin and subcutaneous tissues between the site of primary melanoma and the regional lymph nodes. In-transit metastases are a natural phenomena of melanoma and the incidence increases with Breslow thickness of the primary. We have estimated the incidence of in-transit recurrence from the three randomised controlled trials (RCT) of margin width excision which did not allow either sentinel lymph node biopsy (SLNB) nor elective lymph node dissection (ELND). These trials excluded primary tumours in the head/neck. The three relevant trials [(2,3,4)] suggest that the incidence of in-transit metastases varies from 2.5% (at Breslow thickness 1 mm) to 6.3% (at Breslow thickness 3.1mm). There is evidence to suggest that the incidence of in-transit disease is increased iatrogenically by ELND [(5)] and by selective lymphadenectomy in sentinel node positive patients [(6)]. The explanation for this iatrogenic phenomena is lymphatic obstruction and entrapment of tumour cells en-route to the regional lymph node basin.

In-transit metastasis is associated with a poor prognosis and in the most recent American Joint Committee on Cancer Staging (AJCC) system [(7)] is classified either as Stage IIIb or IIIc, depending on whether it is also associated with regional node metastasis. The ten year survival of patients with in-transit metastases, but without lymph node involvement ranges from 41 to 56% and with nodal involvement this is reduced to 28 to 35% [(8)]. It is the author's experience that the number of deposits increases over time and

that development of accelerated in-transit disease is soon followed by the appearance of distant metastases. Treatment is, therefore, aimed at palliation of symptoms rather than an attempt to eradicate all disease in a vain attempt at cure.

One of the great enigmas of in-transit disease is that its incidence varies by site. Balch et al [9] have suggested the following incidence:

- Proximal extremity 1.1%
- Trunk 3.1%
- Distal extremity 5.3%
- Head and neck 9.4%

There is no benefit to excising in-transit metastases widely. Wide excision of an in-transit metastasis with reconstruction for example by skin graft, local flap or even free tissue transfer is a common error seen in practice.

## Treatment of in-transit metastatic melanoma

This amounts to symptomatic treatment either to eradicate the disease temporarily or to reduce its rate of progress. As stated above, it is the author's experience that with time the number of in-transit foci will increase and the interval of time between the appearance of further foci of disease will reduce. Therefore, initially, complete local excision of the presenting metastasis or metastases (usually few) is the most efficient treatment. More numerous in-transit metastases can be controlled by various treatments including local excision, cautery, cryosurgery and carbon-dioxide laser vaporisation. We and others have found this laser technique to be very useful especially in patients with multiple cutaneous or superficial subcutaneous lesions [10,11]. Laser treatment can be performed either under local anaesthetic as a Day Case procedure or under general anaesthetic, requiring one postoperative night in Hospital depending on the number of lesions lasered. Surprisingly, the treatment is painless and is well tolerated. After laser vaporisation, the wounds are covered by an occlusive dressing which is

then removed by the District Nurse after one week. By that time, most of the lesions are dry and have crusted. The crusts fall off within a few weeks. There are no resource implications with regard to carbon dioxide laser vaporisation because these machines are available in virtually all District General Hospitals being used routinely by Gynaecologists (for cervical dysplasia), by ENT Surgeons (for lesions in the larynx and trachea) and by Dermatologists with an interest in laser therapy, for a variety of conditions. In the author's experience, the regular use of carbon dioxide laser has reduced the need for isolated limb perfusion.

**Isolated limb perfusion (ILP)**

ILP can deliver high doses of cytotoxic agents to a limb while minimising systemic toxicity. The dose delivered regionally can be up to ten-fold higher than the system mean tolerated dose. This logistically and technically complex procedure has potentially wide-ranging complications and should be reserved for disease that cannot be managed by excision or carbon dioxide laser therapy. Briefly, an extra-corporeal circuit is established by cannulating an artery and vein to the limb after obtaining proximal vascular occlusion either by a tourniquet or by Esmarch bandage. ILP inevitably causes local toxicity ranging from mild erythema to extensive epidermolysis and deep tissue damage [(13)]. Compartment syndrome can occur and may require fasciotomy. Systemic leakage of the limb perfusate may produce dose-dependant and agent-specific complications including myelosuppression and hypotension. It is important to stress to patients considering this procedure that only 60% will receive worthwhile benefit. This means control of disease and maintenance of remission for approximately two years. In other words, 40% of patients will risk the complications for no benefit. The usual agent employed in ILP circuits is Melphalan but in recent years the effect of Melphalan has been potentiated by tumour necrosis factor alpha (TNF α). There are no RCTs that have tested Melphalan plus TNF α versus Melphalan alone. However, TNF α, which is a biological agent which targets tumour neo-vasculature, is known to increase response rates and duration of response [(14)].

To increase the number of centres Nationally which can provide a Melphalan plus TNF α service would have resource implications. Currently, the treatment is only offered at the Royal Marsden Hospital and Gartnavel Hospital in Glasgow. However, I believe that a Unit in Hull is being established. If that is the case, then perhaps one other Unit somewhere in central England, would provide an adequate service for the UK. Boehringer Pharmaceuticals will only supply TNF α to Units which have been validated as experienced and competent. They insist that the Surgeon, Anaesthetist, Physicist and Perfusionist all go for induction training to Rotterdam.

Isolated limb infusion is not as potent as ILP because it is performed on an anoxic limb without hyperthermia and it is not possible to use TNF α by infusion.

**Surgical salvage of fungating (usually relapsed) nodal disease**

Relapse of regional node disease following therapeutic lymph node dissection is not uncommon and is a regular challenge. Fungating disease may require excision and reconstruction usually by a locally transposed myo-cutaneous or fascio-cutaneous flap. This is standard treatment which is already provided with the co-operation of Plastic Surgery expertise.

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# Appendix G

# Position Paper on Immunology and Immunotherapy for skin cancer

# Main classes - non-melanoma malignancy - SCC, BCC and Melanoma

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# Non-Melanoma Skin Cancer

Squamous cell cancer (SCC) incidence increases dramatically in immunosuppressed patients in a time dependent manner.

Basal cell cancer (BCC) also increases, but less dramatic. (Ramsey HM, 2002)

## Conclusion

SCC and BCC should be sensitive to appropriate immunotherapy.

Relevance: to lesions that are not easy to remove surgically or to multiple recurrent lesions.

## Possible Therapy

### Imiquimod and derivatives

1. Effective maintained responses to both SCC and BCC in immunosuppressed patients(Aitken, Eklind J, 2003).
2. Mechanism may involve either activating dendritic cells and via TOLL receptors or inducing apoptosis (or both) (Schon M, 2003).
3. Kerato  acanthoma are also reported as responding to topical Imiquimod.(Bhatia, 2004).

# Melanoma

There is a long history of immunotherapeutic approaches in the treatment of melanoma.  This is because of the high rate of relapse following surgery and the ineffectiveness of radiotherapy and chemotherapy to affect survival in the majority of cases.

The first observation of a clinical response to immunotherapy is attributed to Coley, who developed the eponymous 'toxins', which appear to induce a 'cytokine storm' in addition to any other response.

BCG and other non-specific immune modulators have been used for decades to treat melanoma. BCG injected into a melanoma subcutaneous nodule or node will give a response rate of approximately 50% (RR - 20-80%). It is still used by many specialists today to treat non-resectable metastatic lesions.

Note: many elegant gene therapy vectors delivering IFN, etc., intratumourally are no more effective.

BCG has also been used as an adjuvant therapy in stage III patients. There is some controversy of its value - however, in assessing studies, account needs to be made of country (level of TB and BCG vaccination), responsiveness to PPD, strain, dose and number of inoculations given.

Although two randomised trials failed to show any improvement for BCG, chemo alone or in combination in stage III patients, other studies suggest a positive effects in poor PPD responders (Cascinelli N, 1989).

## Vaccines

A large number of vaccine approaches have been investigated over the last two to three decades. They have been used prophylactically after stage III and stage IV resections to try to prevent recurrence, as well as therapeutically.

The main types of treatment tried are:

1. Whole cell vaccines, both autologous and allogeneic.
2. In-vivo modification of these cells by gene transfer constitute the majority of gene therapy trials in cancer. Genes used include most known cytokines and co-stimulatory molecules.
3. Cell lysates, either autologous or allogeneic.

More recently, vaccines have been based on:

1. Gangliosides.

2. Peptides.

3. Heat-shock protein preparations (autologous only).

4. DNA technology.

5. Virus Vectors.

In addition to the above, antigen presentations has been enhanced using ex-vivo expanded dendritic cells (DCs). The autologous DCs (although allo DCs have been used by one group) are expanded ex-vivo and pulsed with cell lysates, peptides, etc., or transfected with RNA before being given to the patient as a vaccine.

DCs have been given through the intravenous, intradermal, intranodal, intratumoural and subcutaneous routes.

**Current Status**

The most advanced vaccine (in development here) in melanoma is based on BCG (for first two injections only) and three allogeneic cell lines developed by Donald Morton of the John Wayne Cancer Institute, California, U.S.A. To date, 2000+ patients have been treated; non BCG associated side effects are seen. Although response rates are under 10% in non-resectable disease, the effect on survival is dramatic in stage IV disease. Patient controlled large phase II studies, especially in surgically resected stage IV with a five year survival, greater than three times non-vaccine treated patients at the same institute, rising to a 40% five year survival in patients with pulmonary metastases (Hsueh EC, 2002).

The vaccine has been acquired by CancerVacTM who are conducting a large multi-centred, randomised, double-blind trial against BCG and placebo vaccine in resected stage III and stage IV disease. 1800 patients are being recruited. Interim analyses shows that overall survival is higher than any previous report. As the trial was not stopped at this time, it can be assumed that BCG + vaccine is not having a negative effect and may be beneficial

relative to this dose and schedule (Note:  BCG dose is determined by PPD reactivity in this study).

## Interferon

At the start of this study, high dose Interferon was used as the control arm. However, following the publication of the E1690 trial showing no overall survival (OS) advantage between high dose (HD) and low dose (LD) Interferon compared with observation.  The authors argued that the observation arm was able to have Interferon on relapse, which totally undermines the argument for adjuvant therapy!  The toxicity of Interferon (hepatitis, depression, etc.) could be argued as acceptable if a significant OS could be guaranteed.  Meta analysis of Interferon trials will suggest increased time to relapse by 2.-3 months, but not improve survival. (Kirkwood JM, 2000)

- Interferon is too toxic for a nil survival advantage to be used outside of a trial.
- Interferon (Alpha) increases HLA expression and enhances NK activity.
- However, these effects revert with continued use (3-4 weeks).

If Interferon is to be pursued in trials it should be used on a pulsed basis, every three weeks.  It may enhance vaccine efficacy if scheduled appropriately.

## Vaccines continued

The next most 'mature' vaccine is the ganglioside vaccine, GM2, developed by Livingstone and colleagues at The Sloane Kettering.  A randomised study using BCG as an adjuvant against BCG alone showed a non-significant trend to increased RFS and OS.  However, if patients with a pre-existing immune response to the ganglioside (induced naturally) and non-responders were omitted from analyses, the vaccine 'effect' was significant.

Progenics developed the vaccine in a phase III study substituting BCG with QS-21 as adjuvant.  However, it performed worse than high dose Interferon.

This may be explained by the fact that BCG induces cell mediated responses (Th-1) whereas QS-21 induces a strong humoural (Th-2) response in addition. This trial highlights the importance of the adjuvant and the balance between Th-1 and Th-2 responses in melanoma vaccine trials.

## Other non-specific vaccines

Mycobacterium vaccae (SRL-172) is related to BCG but differs in that it is not live, but heat killed. It induces clear Th-1 cytokine shift in at least a third of patients and this alone can result in clinical responses. Adding IL-2 in low dose increases the cytokine shift and increases the response rate (approx. 25%). However, in keeping with most vaccines, immune responders survive longer that those who do not (Maraveyas et al., 1999), (Nicholson S, 2003).

The M.vaccae and low dose IL-2 regimen is extremely safe, relatively non-toxic and has led to prolonged responses in advanced non-resectable disease in the lung, liver, skin and lymph nodes. It deserves further investigation at a national level. Unfortunately, SR Pharma do not have the resources to sponsor the necessary trials and Chiron, who make IL-2, are concerned that it is 'off patent' next year. It is worth noting that the clinical response rate and survival are superior to peptide and DNA based vaccines targeting specific CTL responses. This may be explained by the fact that the innate immune system plays a major role in immune surveillance and translating the 'danger' signal with cells, such as NK, NKT, gamma delta and non HLA restricted CD8 cells, all capable of killing tumour cell lines in vivo.

## Other vaccine candidates

A number of studies have used whole cell lysates as vaccines and one of these has been commercialised in Canada (Melacine). A recent trial showed a relapse-free survival advantage in stage II melanoma patients who shared two of five HLA types, particularly A2 and C3 (Sosman JA, 2002).

However, they are not as effective as live (irradiated) whole cell vaccines in their current form (Ravindranath MH, 1997).

**Peptide trials**

Peptide vaccines are made from major shared antigens, such as MAGE, MART, gp100 and tyrosinase. They are HLA restricted and many trials are limited to HLA A2 patients. Patients may make immunological responses as assessed by ELISPOT, tetramer and proliferation studies, often without clinical responses, which are rare. Moreover, effective responses can be 'evaded' with epitope escape occurring.

Peptides are also used to pulse ex-vivo cultured dendritic cells, which are then used as vaccines and this appears to be more effective than 'direct' peptide vaccination. Peptide epitopes are being constructed into viral vectors or DNA based vaccines and several phase I/II studies are ongoing. Epitope escape has resulted in all current /future studies looking at multiple epitopes, e.g. 3 - 5.

Whereas these approaches are associated with induced immune responses and occasional clinical responses, they are not as effective as whole cell based vaccines or when used with dendritic cells.

**Dendritic cell trials**

Dendritic cells (DCs) can be expanded ex-vivo, pulsed with tumour antigen in the form of peptide, mRNA, lysate whole cells or fused with tumour cell lines and then used as a vaccine. As tumour cell lines contain many shared antigens in tumours, such as melanoma, they are a favoured antigen source in several ongoing trials. The cells are allogeneic as it is impractical to growth autologous cell lines for therapy, a fact which became apparent in early gene therapy studies, which grew the cells to transfect IL-2 or GM-CSF into them (the patients died before the vaccine was ready).

Dendritic cell expansion is a bespoke procedure requiring good laboratory practice (GLP) facilities and considerable expertise. Consumables alone cost approximately £3,000 to make a vaccine. Fortunately, it has been possible to adapt the procedure so that pulsed DCs can be frozen successfully so that they are more effective than non freeze/thaw preparations (John J, 2003).

The details of DC preparation are still unclear with few groups/trials using the same protocol. Moreover, it is unclear if the GM-CSF/IL-4 subset is the active subset relative to tumour antigens, which may favour the viral presenting sub-type expressing TOLL-7 receptors. Details of optimum dose, maturation, site of injection, etc., are all unclear for any specific protocol.

DCs should not be considered optimal in their own right and may require 'help', such as low dose IL-2.

**'In-vivo' DC expansion**

The observation that TOLL-7 DCs may be more effective tumour antigens presenters led to the identification of a TOLL -7 antagonist, namely Imiquimod ointment (Aldara).

Coincidentally, there have been anecdotal reports of virtually complete responses of Lentigo Maligna to Aldara (Ahmed I, 2000) which have been confirmed in two cases by the author. It is likely that DCs can be activated over the skin on any palpable tumour mass and a trial using Aldara with intra tumoural IL-2 has commenced at St. George's Hospital, London SW17. Responses to even bulky disease have been observed to date. However, it is too early to see if the induced immune response translates into active systemic control and increased survival.

## Other approaches looking for trial recruitment

Heat shock protein preparations. Antigenics will prepare autologous vaccines from 7 gram of tumour tissue. This excludes most melanoma patients, not only is it an expensive bespoke processes and impractical for most melanoma cases, but it is also remarkably ineffective clinically, compared to its pre-clinical testing.

**Medarex MAB against CTLA-4**

Currently low response rate and high toxicity.

**Coley - Promune targets TOLL 9 receptor.**

Some response 2/20, side effects.

**Vical - Allovectin, gene therapy into tumour.**

10% response rate.

**Celgene - '5013 'imids'**

Randomised trial against no treatment arm. Stopped with no obvious effect. However, good responses seen in fit phase II patients who had previously had immunotherapy. New protocols are being written.

## Ongoing Treatment Issues

### Stage III fully resected patients

In the absence of an effective therapy and the CancerVax trial, soon to be fully recruited, there is an urgent need for another national trial.

- Candidates include BCG (dose titred) with or without COX-2 inhibitors, IFN pulsed three weekly, instead of every other day, and GM-CSF as a matched study, has shown a three-fold median survival advantage with low dose therapy over no treatment (Spitler LE, 2000).
- Ganglioside vaccines clearly need further development before any further stage III trial is started.
- 'Peptides' need to be multi-epitope and not require HLA selection to be practical.
- DC based vaccines are too expensive and 'immature' for adjuvant studies.

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# Appendix H

# SYSTEMIC TREATMENT OF MELANOMA

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# BACKGROUND

Patients with metastatic melanoma are incurable and have very poor life expectancy with a median survival of 6-8 months. Some metastatic sites are associated with a better prognosis for instance median survival is 7-11 months for those with lung secondaries, skin nodules outside the local region or distant lymph node involvement. In contrast, patients with disease in the brain or liver have only a 2-5 months median survival[1].

A number of prognostic factors, have been developed that identify those with primary disease or locoregional lymph node involvement who are risk of a systemic relapse. These include thickness and ulceration of the primary and in the case of locoregional lymph node involvement, the number of lymph nodes affected[2]. The finding of melanoma cells in the sentinel node is another very powerful prognostic factor for patients with 1-4mm thick primary lesions[3-8].

This ability to identify a group of patients who are at high risk of relapse, coupled with the incurability of metastatic melanoma has lead to a number of different treatment strategies being explored in the adjuvant setting in an attempt to alter the natural history of this condition.

Metastatic melanoma is an area of oncology that desperately needs new and effective therapies.

# ADJUVANT THERAPY

## Chemotherapy

A number of randomised trials using chemotherapy were performed in the 1980s including one utilising high dose chemotherapy[9-19]. There is no evidence from randomised studies that chemotherapy has any role in the adjuvant setting and the major international trials organisations do not use it in their control arms. Furthermore, there have been very few randomised trials in the last 10 years that have used cytotoxics alone in the experimental arm.

### Interferon alfa

There have been 11 randomised trials examining the role of interferon alfa as adjuvant treatment[20-30]. Interferon alfa has a wide range of toxicities which can be debilitating and are dose-dependent. Two trials have shown an overall survival benefit; these studies utilised high doses of interferon alfa and one of the trials compared high dose interferon to a vaccine[20,29]. Recently, these 2 high dose trials have been updated and with longer follow-up, the overall survival benefit in one has disappeared and in the other the statistical significance has become borderline ($p = 0.04$)[31].

There is however, one consistent benefit that is shown in trials and it relates to recurrence-free survival. This advantage appears to be associated with low dose schedules as well as high dose regimens. Convention and regulatory considerations have up to now, disregarded this endpoint as relevant to adjuvant therapy. However, recently the FDA and indeed many in the oncological community, have started to consider recurrence-free survival as a valid endpoint for adjuvant trials in some tumour types.

A comprehensive meta-analysis of the data on adjuvant interferon alfa has been published by Wheatley[32]. It demonstrates a dose-independent impact of interferon alfa on recurrence-free survival and a nonsignificant trend to benefit for overall survival.

The final results from two large studies performed by the EORTC are awaited (Protocols 18952 and 18991).

## Immunotherapy

Vaccine therapy is an attractive strategy because melanoma is an immunogenic tumour that is associated with well documented immunological phenomena, e.g. vitiligo. In addition, vaccine therapy unlike interferon alfa is non-toxic and well tolerated.

There are 7 randomised trials of different vaccines and none have demonstrated an overall survival benefit although some have shown

improvements in recurrence-free survival[29, 33-38]. There are reports that show patients who mount an immune response to a vaccine live longer than those who fail to mount a host reaction[34,39-41]. There are also subgroup analyses suggesting that some patients obtain a survival benefit from vaccination by virtue of their HLA type 42.

There are a number of different vaccine strategies in development worldwide and there is no particular frontrunner. The international consensus is that vaccine therapy is an important area of research but is not standard of care.

# METASTATIC DISEASE

There has never been a treatment for metastatic melanoma that has demonstrated an overall survival benefit. However, objective response can be obtained and these can benefit patients in terms of symptom control.

A number cytotoxic drugs have activity and since the early 1970s randomised trials have been performed. The role of single agent and combination chemotherapy [43-47], chemotherapy plus tamoxifen48-51, chemotherapy plus interferon alfa[52-57] and biochemotherapy (chemotherapy plus IL2 +/- interferon) [58-63] have all been examined.

There are no randomised trials that support the use of IL2, interferon, adoptive immunotherapy or any combination of these[64-68].

Vaccines can induce host immunological responses and objective tumour regressions [69]. Survival benefits have only been demonstrated when historical controls have been used [70].

The results of these trials have been summarised in a number of review articles over many years and there is now a consensus that there is no intervention that has been shown to be superior to single agent DTIC1,71-75 This drug in randomised trials has a response rate of only about 10%  but it is cheap, convenient to deliver (short iv administration  time on a 3-weekly schedule) and is very well tolerated when given in conjunction with a 5-HT3 receptor antagonist.

# CEREBRAL METASTASES

The prognosis of patients with cerebral metastases is particularly poor (median survival 3-4 months). A small percentage of patients will survive 1-2 years, these patients tend to have solitary lesions.

There is a paucity of randomised data in this area [76-80]. Most information comes from single arm phase 2 studies or retrospective institutional series [81-86].

There is a consensus that treatment is unsatisfactory, however generally guidelines are as follows:

- patients with solitary lesions should have them removed surgically if technically feasible and clinically appropriate. There is no consensus regarding the role of radiotherapy after surgery.

- palliative care alone should be considered for those with a poor performance status and/or neurological deficit that is not significantly reversed by steroids. Similarly, careful consideration needs to be given to the benefits/morbidity of treatment for those who have multiple sites of disease.

- there are no randomised data that inform the debate as to the best treatment modality, radiotherapy or chemotherapy.

- temozolomide and nitrosoureas such as fotemustine are reasonable chemotherapy choices [87-90]. Fotemustine has been compared to DTIC in one of the few randomised trials in this situation and a benefit in favour of fotemustine was shown (response rate in the brain 5.9% vs. 0%; median time to brain metastases in those without involvement at this site at study entry was 22.7 months vs. 7.2 months, p = 0.06) [80].

- whole brain radiotherapy is the standard field [91-95]. However, there is no consensus concerning the best fractionation schedule.

- targeted radiotherapy such as stereotactic techniques or gamma knife are recommended by some where it is available and the size and number of lesions make such methods appropriate.

- there is evidence from one randomised trial that the addition of fotemustine to radiotherapy increases the time to cerebral progression [76].

This subject is very well reviewed by Stevens and Fife [96].

# SERVICE GUIDANCE

## General

There have been a number of evidence-based guidelines published in different countries. Guidelines published in Australia are often quoted and are very helpful [97]. There are 2 main UK guidelines that have been published: one from Scotland and the other from the UK Melanoma Study Group and British Association Dermatologists [98,99]. There are few major differences between these documents in relation to guidance on best practice.

The principles of good service configuration for melanoma do not differ from those that are applied to other tumour types. All aspects of diagnosis and treatment should be carried out by those who have training and expertise in this tumour type. Melanoma differs from other tumour types in that patients are cared for by very different disciplines at different stages of the disease. For instance, patients with primary disease require a dermatologist and the availability of a plastic surgeon whereas those who present with/develop metastases do not require the skills of a dermatologist but should be cared for by nonsurgical (medical/clinical) oncologists with a special interest in melanoma. They also need access to a specialist melanoma surgeon if palliative surgery is required.

The organisation of the care of patients with primary cutaneous melanoma needs to be seen in the context of other primary skin cancers. These patients are best treated by a team of dermatologists/plastic surgeons/pathologists specialising in skin cancer. This is probably the most efficient way of organising scarce resources such as expert pathology. In certain specialist centres there may be a division by skin cancer type with pathologists and others, sub-specialising in different types of skin cancer.

## Personnel

The training of surgeons with a special interest in melanoma has tended to be the province of plastic surgery. This will continue and should be encouraged. However, although access to plastic surgery should be mandatory for any melanoma team, there are surgeons in the UK who have not had a complete

plastics training who specialise in the disease. This is also the case in a number of centres in the US and mainland Europe. These surgeons often also specialise in sarcoma and are in reality, surgical oncologists specialising in soft tissue tumours. It is important for the surgeons in the team to be knowledgeable about melanoma not simply to have expertise in the surgical techniques employed in the management of this disease.

Patients with mucosal head and neck melanomas and melanomas of the female genital tract are often under the care of head and neck/gynaecological oncology surgeons. This practice should continue as many of the issues relating to the care of these patients relate to the site specialisation of these surgeons. In addition, head and neck surgeons and gynaecological oncologists during their training are taught about melanomas of this region and have competence in this area. However, these surgical teams should also seek the advice of the team in their network that cares for patients with cutaneous melanoma. The nonsurgical oncologists on the cutaneous melanoma team need to lead on advice about adjuvant therapy and should take over the care of those with metastatic disease.

The precise role of radiotherapy in the management of melanoma is unclear however, it is important that cancer centres/networks have a clinical oncologist who specialises in this tumour type and is an integral member of the melanoma team. The clinical oncologist should develop links with his/her colleagues on the Head and Neck and Gynaecological Oncology Units to allow patients with noncutaneous melanoma to have the best advice, i.e. from those who are site-specialised and the individual who has specific expertise in melanoma.

It is important that patients with metastatic disease have access to a nonsurgical oncologist who has a specific interest and expertise in the management of disseminated melanoma. This is usually a medical oncologist but this is not mandatory as there are clinical oncologists who have made this tumour type their particular specialty. Nonsurgical oncology input into the team should be mandatory and integral.

## Organisation

The organisation of the specialties that are concerned with the care of melanoma patients is complex and may differ from network to network. Primary patients may require the input of a plastic surgeon or clinical oncologist and these specialists should be present at multidisciplinary meetings where such patients are discussed. Unit/centres with large numbers of primary patients should be allowed to conduct multidisciplinary meetings without the presence of nonsurgical oncologists who specialise in metastatic disease. Similarly, there is little point in dermatologists being present at multidisciplinary meetings where large numbers of patients with metastatic disease are presented but there are patients with metastatic disease who require surgical intervention and there needs to be multidisciplinary meetings where surgeons are present so that these patients can be discussed.

Therefore, networks need to configure their multidisciplinary meetings according to specific patient needs. It is unrealistic to have one MDM a week at which all skin cancer patients are discussed with all specialists present. The most practical model for nonmelanoma skin cancer and/or melanoma multidisciplinary meetings in networks is one that resembles overlapping Venn diagrams where the overlapping sections represent multidisciplinary meetings with the necessary disciplines are present for particular groups of patients.

multidisciplinary meetings for patients with noncutaneous primary melanoma sites (ocular, head and neck and female genial tract) should initially be dealt with within the appropriate unit, i.e. one of the specialist ocular melanoma units in the UK, or the regional Head and Neck or Gynaecological Oncology Unit. This is because the management of these patients is largely surgical but with radiotherapy input and is very much site-based. The nonsurgical oncologist specialising in systemic therapy needs to be consulted and if necessary take over the care of the patient if adjuvant treatment is going to be considered or if the patient develops metastatic disease.

## Future

The major future change in the management of patients is likely to be centred on the issue of sentinel node biopsy. In a number of countries this has become standard of care although there is no evidence that this procedure benefits patients in terms of disease-free or overall survival. Nevertheless, this technique is being performed in some centres and the availability of sentinel node biopsy needs to be standardised across the country. One suggestion would be that each network/centre would designate a sentinel node biopsy team and that they should perform the sentinel node biopsies for the network/centre. These procedures however, should only take place within the context of clinical trials that have been through the usual approval procedures, i.e. LREC/MREC.

Some areas of the country do not have nonsurgical oncologists whose main interest is melanoma and these areas need to be identified and this deficiency addressed.

The results of systemic treatments for melanoma are very disappointing. It is an area of oncology that desperately needs more research so that new active therapies can be developed. It is important that in each network the melanoma service is closely linked into a research programme so that patients can be offered entry into clinical trials and patient material can be fully utilised in translational projects.

Prevention campaigns and early diagnosis programmes need to be instituted and co-ordinated throughout the UK and the organisation of this should be through the networks. Networks need to set up melanoma awareness programmes linked with current arrangements for the rapid diagnosis of pigmented skin lesions so that melanoma can be diagnosed early. The mortality from this is then likely to be reduced. Early diagnosis campaigns have been shown to reduce mortality in Australia.

## Conclusions

It is important that service arrangements throughout the UK are flexible and take into account local circumstances such as geography. However, the

principles of having a specialist melanoma team in each network should be mandatory. The core team needs to consist of individuals who have specialist training and expertise in the following aspects of melanoma diagnosis and treatment: histopathology, dermatology, plastic surgery, nonplastics melanoma surgery (in some areas), clinical oncology and the delivery of systemic treatment (usually a medical oncologist). Those units that have a nonplastic surgery-trained melanoma surgical specialist should still have access to specialist plastic surgery. MDM arrangements may need to be flexible but the basic principles of MDM working should be adhered to, i.e. patients with problems that require input from more than one discipline should be discussed in a forum that consists of those with the appropriate expertise to advise on the optimal management for that patient.

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# Appendix I

# Position paper at the request of the National Institute for Clinical Excellence

# A consideration of conventional surgery and conventional histopathological assessment and Mohs micrographic surgery in the treatment of basal cell carcinoma and squamous cell carcinoma of the skin

(to be read together with reference 22 ‘The case for other surgical options’, Key Advances in the Clinical Management of Skin Cancer, Royal Society of Medicine Press, 2004 )

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# Introduction

Complete surgical excision may be regarded as the optimal treatment for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin. Surgical excision gives the histopathologist the opportunity to assess resection margins for clearance laterally and in depth.

Incomplete excision of BCC or SCC will on the balance of probabilities lead to local recurrence [1,2] , and therefore re-excision of incompletely excised lesions is usually advised.

In the early part of the 1900s radiotherapy and conventional surgery for often advanced lesions was followed by disease recurrence often enough for Mohs to introduce his technique of histologically controlled tumour excision, with the principles that the whole of the excision edge was monitored histologically until no tumour was seen in the 'slice' of tissue and clearance was thus determined.

Since Mohs original work in the 1930s, those who advocate Mohs technique have repeatedly suggested it is superior to conventional surgery because it

a) more completely examines the resection edges

b) is thus associated with a lesser rate of local recurrence

c) sacrifices less normal tissue than conventional surgery

However these claims are against a background of poor documentation in the literature of the results of conventional surgery – particularly lack of minimum 5 year follow-up studies and failure of published works to document the incidence of incomplete excisions and give information on the re-excision rate of such cases.

Thus the perceived 'poor' results for conventional surgery may well relate to those incompletely excised lesions that were not re-excised. The problems in reported series are illustrated thus:

- Koplin and Zarem [3] observed that ' a major difficulty in analysing recurrent BCC is the paucity of studies relating recurrence to adequacy of the original excision'.

- Emmett [4] wrote 'various papers in the literature which have noted recurrence fail to mention the histological type of basal cell carcinoma and the margin of clearance in millimetres'

- Bart et al [5] candidly recorded 'excised specimens were not routinely examined for adequacy of all surgical margins'

- Silverman et al [6] who reported a cumulative 5 year recurrence rate for 588 surgically excised BCCs of 4.8% but failed to record the proportion that were primarily incompletely excised, nor gave information as to whether or not incompletely excised lesions were re-excised.

## Conventional surgery and histological assessment

It is unlikely that the current standards of conventional surgery and histological assessment can be equated with those reported by different authors over the last 50 years [7,8]. Reviews of conventional surgery for BCC and SCC lack critical analysis of publications, specifically no detail on the incidence of incomplete tumour excision in most series and the significance of this on interpreting outcome [9,10,11,12,13,14]. These reviews do not allow the fate of completely excised (by conventional surgery) BCC and SCC to be known.

## A) Basal cell carcinoma

### 1) Primary basal cell carcinoma

Conventional surgical excision of basal cell carcinoma has been reported to give complete excision (as judged by conventional histological assessment) in some 95- 96% of cases with surgical margins of 2mm – 3 mm [15,16]. Margins of 3 or 4mm [17] ,or 2-5mm for localised lesions and 6 – 10mm for infiltrating lesions [18] have also been proposed. Loupe magnification is increasingly advocated as an aid to judging tumour margin [18,19,20,21,22].

Conventional surgery and conventional histological assessment will fail to detect discontinuous tumour, which theoretically could give rise to tumour 'recurrence' .

Recurrence rates over differing time scales after complete conventional excision of BCCs have been given as 0.35% - 1.9% [18,23,24]. Griffiths [22] reported over 1300 completely excised BCCs with potential minimum 5 year follow-up recording 0.35% probable (contiguous) recurrences and 0.6% possible recurrences (nearby- within 1cm, but separate from scar or graft). It was assumed that all recurrences would have been referred back to the primary surgeon.

[Adjusting these figures for 40% loss due to deaths from other causes in the 5 year follow-up [25], the figures for determinate cases would be probable 0.6 % , possible 1.1 %, and a total 1.7 %.] Of course not all will be recurrences and some will represent new primary tumours [26,27]

**2) Recurrent basal cell carcinoma**

After conventional surgical excision of recurrent (previously treated) BCC , recurrence rates of 5% - 12% have been recorded [6,28]. Rowe et al [10] in a review of > 5 year follow-up of treated recurrent lesions found 91/522 (17.4%) recurred, but it is not recorded if they had all initially been completely excised.

**3) Incompletely excised basal cell carcinoma**

On the balance of probabilities (> 50%) tumour will be found when the site of an incompletely excised basal cell carcinoma is re-excised by conventional surgery and assessed by conventional histo-pathology [30]. If observed a majority will recur [2] with 18% of recurrences occurring 6 – 10 years later [29]. Re-excision, irradiation or long term follow-up > 5 years are indicated, with re-excision being the most expedient and possibly most cost effective [30] .

## B) Invasive squamous cell carcinoma

#### 1) The primary squamous cell carcinoma

Long term follow-up shows that 40% of patient die within 5 years of SCC excision of unrelated disease. Thus in any series 60% of patients will be determinate i.e. surviving 5 years with or without disease or dying within 5 years of SCC.

Griffiths [22] reported 150 determinate cases after conventional complete surgical excision for the 10 years 1988 – 1997 followed for 5 years. Median tumour thickness was 3.1 mm.

There was one probable local recurrence 1/150 (0.7%) under a skin graft (initial deep clearance 0.9mm) in an immuno-compromised patient 12 year after a renal transplant.

Two possible local recurrences occurred (adjacent but not contiguous with scar or graft). Thus total probable and possible local recurrence rate was 3/150 (2%).

Rowe et al [11] summarise for 124 patients a recurrence rate of 8.1% but without information of the number that had been incompletely excised. Immerman et al [31] gave the rate as 7%.

### 2) The recurrent squamous cell carcinoma

For 34 cases recurrent after previous treatment with > 5 year follow-up Rowe et al [11] reported a 23% local recurrence rate , but details of completeness of excisions are lacking.

### 3) The incompletely excised squamous cell carcinoma

25% - 50% of these will recur if not re-excised and just observed [1,31]

### 4) Metastases

After conventional surgical excision of primary SCC over 5 year follow-up metastasis rates of 11% -13% have been recorded [22,31,32]

## Mohs micrographic surgery

This technique has been modified from the original descriptions of particular fixation to a fresh tissue technique and ‘fast’ and ‘slow’ Mohs. However regardless of these variations the principle is that after curettage of the main tumour bulk sequential slices of the deeper and peripheral tissues are taken and examined for tumour until a totally tumour free plane is reached.

The technique as with conventional surgery is unlikely to detect discontinuous tumour. The horizontally orientated tissue slices are variously described in thickness as 1-2 mm [33], 1-3 mm [34,35,36,37], 3mm [38].

The technique may be confounded by false negative tumour free margins [39], and when recurrences occur after Mohs surgery 22% occur more than 5 years after primary treatment [40]. The limitations of Mohs micrographic surgery that may explain subsequent tumour recurrences have been discussed [35,38,41,42,43]

Some authors appear to recommend the excision of 2-5 mm or 5 – 10mm of apparently normal tissue around the tumour to ensure clearance [34,44]. Wolf and Zitelli [45] indicated 4mm margins would eradicate 95% of cases.

Only one 5 year follow-up study has been identified in the UK literature [46], with small numbers. Other reports are for small numbers and limited follow-up [47,48,49].

## A) Basal cell carcinoma

### 1) Primary basal cell carcinoma

5 year follow-up recurrence rates range 0.7% - 6.5% [46,50,51] and for other non uniform follow-up periods recurrence rates ranging 0.5% - 6.8% [52,53,54,55]

### 2) Recurrent basal cell carcinoma

Recurrence rates for 5 year follow-up range 4.8% (4/83) [46] 5.6% [10], 6.9% [56], 7.8% [57] ,10% [51]; with 5.6% [54] for average 6 year follow-up and 12% [28].

### 3) Incompletely excised basal cell carcinoma

When the sites of incompletely excised basal cell carcinomas are re-excised using Mohs technique residual tumour will be found in > 50% of cases [58]

## B) Invasive squamous cell carcinoma

### 1) Primary squamous cell carcinoma

Brodland and Zitelli [59] suggested 4mm margins of normal tissue be excised around tumours. Minimum 5 year follow recurrence rates range from 4.8% [54] 5.6% [50], and 3.6% for peri-ocular lesions median follow-up > 5 years [60]

A report from the United Kingdom [61] reported 61 patients with 3.4 years mean follow-up with 2 ( 3.2% ) local recurrences and 3 cases of metastases to lymph nodes 3/61( 5%); their median tumour thickness was 2.0 mm

### 2) Recurrent squamous cell carcinoma

Reported recurrence rates are 10%, 11.9% , 37% [11,54,62] but follow-up periods were not uniform.

### 3) Incompletely excised squamous cell carcinoma

25%- 50% of these will recur if not re-excised [1,31]

### 4) Metastases

After Mohs excision of SCC the metastasis rates reported are 5% 13% [61,63] but both series had less than 5 years of follow-up.

## Discussion

## Basal cell carcinoma

Recurrence rates after conventional surgery (and confirmed complete excision by conventional histological techniques) for primary basal cell carcinoma are (0.35% - 1.9%), and for Mohs therapy(0.7% - 6.5%) , although the higher figures for Mohs recurrences exceed 5%.

Lawrence [64] concluded ''for primary BCCs attempted single complete excision generally produces cure rates equivalent to Mohs surgery''.

Regardless of excision technique 18 % - 22%of recurrences will occur > 5 years after primary treatment [29 40].

For recurrent BCC treatment Mohs technique had recurrence rates ranging 4.8% - 12%, and whilst Rowe et al [10] recorded an aggregate 17.4% recurrence rate after conventional surgery information on the histological completeness of excision was wanting.

Both conventional surgery and Mohs technique reveal > 50% residual tumour when incompletely excised BCCs are re-excised [30,58]

## Squamous cell carcinoma

Primary squamous cell carcinoma recurrence rates were 0.7% - 2% for conventional surgery and 3% - 10% Mohs therapy. **The theoretical advantages of Mohs extensive margin assessment do not in practice lead to lesser rates of recurrence.**

Some squamous cell carcinomas metastasize to regional lymph nodes and neither conventional surgery or Mohs therapy prevents this in up to 13% of patients. No difference can be discerned between the two therapies in this regard.

### Margins

No method of assessing resection margins for clearance is perfect [65]. If BCCs are resected with a margin > 0.75mm recurrence may be unlikely [66] , although the defined 45% error in marking a 2mm margin is to be acknowledged when interpreting studies on measured surgical margins [67].

### Regression

The assessment of the results of any treatment for BCC should acknowledge that with both primary and residual tumour spontaneous clinical regression can occur [68,69].

## Conclusions

1. Both conventional surgery and Mohs technique  can be associated with tumour recurrence of BCC and SCC.

2. The particular advantage claimed for Mohs technique for treating recurrent BCC and SCC is unclear with recurrence rates of 4.8% - 12% for BCC and 10% - 37% for SCC.

3. It is misleading to suggest that one technique is superior to the other. The biological variation of tumours, including the phenomenon of discontinuous growth for BCC, means that neither technique will eradicate tumours 100%. However the claims that the limited histological sampling of resection margins with conventional surgery must be associated with a high local recurrence rate are not confirmed on careful analysis of the limited information in commonly cited studies

4. There is no evidence that either technique is superior to the other with regard to metastatic spread of SCC.

5. Several reports suggest that as practised by some micrographic surgeons, the technique successively removes 3mm slices of tissue, and in these cases the possible resection margin of normal tissue may be similar to that described for conventional surgery. No studies have been identified which demonstrate that the tissue sacrifice with Mohs technique is less than that seen with conventional surgery.

6. A lack of critical analysis of the variable quality reports over 40 years has potentiated misleading views of the efficacies of both techniques.

7. If no clear differences in 5 year recurrence figures are evident, the choice of either technique should be made on other grounds

8. such as, comparative cost, patient acceptability ( tolerance of the two different types of surgery, and for varying cosmetic outcome)

9. Reports and guidelines should more precisely differentiate between surgical and histological margins being recommended. Acknowledgement of the measurable errors inherent in clinical margin marking ,and the relationship between primary and secondary tissue shrinkage and thus differences between clinical and histological clearance margins, would assist in the debate over presumed optimal clearance margins.

10. If all dermatologists and surgeons involved in the management of non-melanoma skin malignancy would publish their long term results, our present guidelines [70,71] would have a sounder and more robust evidence base, relating to current rather than historic clinical practice.

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# Appendix J

# SKIN CANCER GUIDANCE DEVELOPMENT GROUP

(Prepared for the National Institute of Clinical Excellence)

# Organisation of Services for the Diagnosis and Management of Cutaneous Lymphoma

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# Introduction

Two publications are relevant to develop guidelines for cutaneous lymphoma. The Royal College of Pathologists Minimum Dataset for Lymphoma and the joint British Association of Dermatologists (BAD)/UK Skin Lymphoma Group Guidelines for the management of primary cutaneous T-cell lymphoma (CTCL).[1] In addition the NICE Guidelines "Improving Outcome in Haematological Cancer" are relevant though not specifically concerned with cutaneous lymphoma.

Cutaneous lymphoma is a rare cancer with an incidence of only 0.4 x 10^5 per year. However the great majority are low grade malignancies with prolonged survival and therefore the prevalence is higher. Unlike other lymphomas, the great majority of patients require skin directed therapy and not systemic chemotherapy which is reserved for patients with advanced disease. Skin-directed therapy is not used in other types of lymphoma and includes treatment such as phototherapy (supervised by a Dermatologist) topical chemotherapy or superficial radiotherapy (supervised by a Clinical Oncologist).

Cutaneous lymphoma can be classified according to the new WHO classification [2] and using the EORTC Cutaneous Lymphoma classification.[3] There are minor differences between the two systems in the classification of T-cell lymphoma and more major differences in the classification of cutaneous B-cell lymphoma. These differences have been reviewed [4] Although WHO is not an organ based classification it is still useful to record the presenting anatomical location of any lymphoma and this has been allowed for in the MDS for lymphoma produced by The Royal College of Pathologists. The histological diagnosis of skin lymphoma is a specialised field and has been included in the *National Pathology Specialised Services.* However there is no national provision for specialised clinical services such as total skin electron beam radiotherapy, or photopheresis.

## Clinical and Diagnostic Aspects

A primary cutaneous lymphoma is defined as a lymphoma arising within the skin without evidence of systemic spread at presentation. Approximately 30% of cases are B-cell and the remainder are T-cell with a few NK-cell lymphomas. The commonest type of cutaneous T-cell lymphoma is mycosis fungoides which accounts for approximately 70% of all cases of CTCL. Patients usually present with cutaneous patches or plaques (Stage I disease) which usually remains confined to the skin but can progress to tumours (Stage IIb disease), erythroderma (Stage III disease), nodal disease (Stage IVa) or visceral involvement (Stage IVb). Prognosis in CTCL varies widely depending on subset and stage. Thus, patients with lymphomatoid papulosis or Stage Ia mycosis fungoides have a virtually normal life expectancy whereas patients with CD30-negative large cell lymphoma, or Sezary syndrome, have a median survival of < 5 years. Clinical and pathological expertise is therefore crucial in establishing the correct diagnostic category for implementation of appropriate therapy. In addition molecular analysis of tumour tissue provides valuable diagnostic information and molecular analysis of blood and lymph tissue can provide valuable prognostic information in patients with mycosis fungoides.[5,6]

Similar principles apply to other types of cutaneous lymphoma. Whereas patients with marginal zone B-cell lymphoma or immunocytoma have a 5 year survival of 100%, those with blastic NK-cell lymphoma have a 5 year survival < 20%. Thus all patients with cutaneous lymphoma should undergo diagnostic biopsies for histology, immunophenotyping and molecular studies and the results correlated with a clinical presentation.

## Organisation of Services

The diagnosis of cutaneous lymphoma requires a level of expertise that is not normally available outside of the Cancer Centre. It should certainly not be undertaken by GP's with a special interest. However cancer units have a valuable role to play as skin directed therapy such as photo therapy requires multiple hospital visits which are best undertaken by the local Cancer Unit.

For patients with early mycosis fungoides, a shared system of care between the Cancer Centre and the Cancer Unit would seem an appropriate model. Equally patients with nodular B-cell lymphoma could be managed with annual visits to the Cancer Centre and intermediate follow-up locally.

Management in a specialised centre is required for rare types of cutaneous lymphoma and for patients with more advanced disease. There are approximately 300 new cases of cutaneous lymphoma annually in the UK so very few Specialists have experience or expertise in this area. In addition specialised facilities such as photopheresis for the treatment of erythrodermic CTCL, or Total Skin Electron Beam (TSEB) Radiotherapy are available in only a handful of centres in the UK. Rather than dispersing this expertise more widely it would seem more appropriate to support a system of supra-regional units so that the expertise can be concentrated where the treatment facilities are available and so that tertiary referral centres can undertake clinical studies based on a meaningful number of patients.

In the UK Guidelines for CTCL, it has been proposed that all patients should be seen by a multi-disciplinary team (MDT) in a Cancer Centre with the possible exception of patients with lymphomatoid papulosis (LyP) or Stage Ia mycosis fungoides.[1] However molecular analysis can still be of value in the diagnosis and prognosis of patients with Stage Ia mycosis fungoides, [5] so an initial visit to a Cancer Centre with follow-up by a Cancer Unit would still seem an appropriate model of care for this type of patient. The UK Guidelines propose that the MDT should comprise a dermatologist, a clinical oncologist and a dermatopathologist with expertise in cutaneous lymphoma. The NICE Guidelines *Improving Outcome in Haematological Cancers* recommend that all lymphoma cases are managed by an MDT with a haemato-oncologist as the lead clinician. This would be appropriate for systemic lymphomas with cutaneous involvement, i.e. secondary cutaneous lymphoma, but would not provide optimal care for most patients with primary cutaneous lymphoma since these are usually managed using skin directed therapy supervised by a Dermatologist, or superficial radiotherapy supervised by a Clinical Oncologist.

Clinical trials have shown that early intervention in mycosis fungoides using multi-agent chemotherapy does not improve survival but does increase morbidity [7]. The argument that all patients with lymphoma will require chemotherapy eventually is also not applicable to cutaneous lymphoma. The principle underlying management of indolent primary cutaneous lymphomas should be conservative and incremental. Input from a haemato-oncologist should be reserved for patients that have failed skin directed therapy and require chemotherapy or transplantation. A programme of autologous, and in some cases allogeneic transplantation is being developed for tumour stage MF and other CTCL variants of poor prognosis .[8,9] Clearly the input of an expert Haemato-oncology Unit is essential in this situation, but again the procedure should be limited to designated centres in the UK. In London for example a transplant programme for tumour stage MF is run jointly by the MDT at the St John's Institute of Dermatology, and the Dept of Haematology at the Hammersmith Hospital.

# Recommendations

## Diagnosis and staging.

- Histological immunophenotypic and molecular analysis should be performed on all tissue samples
- Patients should be classified according to the WHO classifications supplemented by the EORTC Cutaneous Lymphoma classification for T-cell lymphoma
- Initial staging CT scans are required in all patients with the exception of Stage I mycosis fungoides and LyP.
- Peripheral blood samples should be analysed for evidence of blood involvement by lymphoma. This includes molecular analysis, lymphocyte subsets and appropriate viral serology (EBV or HTLV-1), protein electrophoresis, serum LDH and Sezary cell counts should be undertaken as appropriate

- Bone marrow aspirate and trephine biopsies are required for complete staging of all patients with B and NK-cell lymphomas and for patients with **CTCL** variants and late stages of mycosis fungoides (Stage IIb or above), but not for Lyp and Stage 1/11A MF

## Management

- An MDT for cutaneous lymphoma should comprise a Dermatologist, a Dermatopathologist and a Clinical Oncologist. Close liaison should be maintained with a Haemato-oncologist as appropriate.

- All patients with the possible exception of early stage mycosis fungoides (Stage Ia) and lymphomatoid papulosis should be reviewed in an appropriate MDT with confirmation of the diagnosis and to establish management strategy.

- Skin directed therapy is appropriate treatment for patients with low grade indolent B-cell lymphomas and early stages of mycosis fungoides. This can be jointly managed between the Cancer Centre and the Cancer Unit.

- Patients with other types of cutaneous lymphoma and those with later stages of mycosis fungoides (Stage IIb or above) should be managed in a Cancer Centre.

- Facilities such as photopheresis and total skin electron beam should be concentrated in selected supra-regional units with the necessary expertise and personnel.

- New agents such as Bexoratene and Ontak offer important therapeutic alternatives and should be evaluated in these selected centres.

- Chemotherapy should be reserved for patients with advanced disease. A programme of autologous and /or allogeneic transplantation should be undertaken by designated centres in the UK, with maintenance of

close liaison between the MDT for cutaneous lymphoma and the transplant centre.

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