



## **Improving outcomes for people with skin tumours including melanoma: Evidence Update October 2011**

**A summary of selected new evidence relevant to the NICE  
cancer services guidance manual 2006 (partially updated 2010)**



Evidence Update 1

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the likely impact. Any new evidence that impacts current guidance will be notified to the appropriate NICE teams. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page ([www.evidence.nhs.uk/topic/skin-cancer](http://www.evidence.nhs.uk/topic/skin-cancer)). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

**Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations. They do not consider economic evaluations.**

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## Introduction

This Evidence Update identifies new evidence that might generate future change to the practice laid out in the following reference guidance:

- **Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance (2006; partially updated 2010). Available from [www.nice.org.uk/CSGSTIM](http://www.nice.org.uk/CSGSTIM)**

Almost 3000 pieces of evidence were identified and assessed of which 20 were selected for the Evidence Update. An Evidence Update Advisory Group, comprised of subject experts, has reviewed the prioritised evidence and provided a commentary.

## Other relevant accredited guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:



Skin cancer prevention: information, resources and environmental changes. NICE public health guidance 32 (2011). Available from [www.nice.org.uk/guidance/PH32](http://www.nice.org.uk/guidance/PH32)



Marsden JR, Newton-Bishop JA, Burrows L et al. (2010) Revised UK guidelines for the management of cutaneous melanoma (NHS Evidence accredited). Br J Dermatol 163:238–56.

Available at

[www.bad.org.uk/Portals/\\_Bad/Guidelines/Clinical%20Guidelines/Melanoma%20guidelines%202010.pdf](http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Melanoma%20guidelines%202010.pdf)

## Feedback

If you have any comments you would like to make on this Evidence Update, please email [contactus@evidence.nhs.uk](mailto:contactus@evidence.nhs.uk)

## Key messages

The following table summarises the key messages to be taken from the Evidence Update. It also indicates whether new evidence identified by the Evidence Update has potential to impact the current guidance listed in the introduction. The relevant NICE teams have been made aware of this evidence which will be considered when guidance is reviewed.

For further details of the evidence behind these key messages and the specific guidance which may be affected, please see the full commentaries.

Key message	Potential impact	No impact
<b>Organisation of skin cancer services</b> <ul style="list-style-type: none"> <li>GP-led melanoma follow-up cannot be fully supported over attending at hospital. Despite reports of greater patient satisfaction, current data are not robust enough</li> </ul>		✓
<b>Risk factors</b> <ul style="list-style-type: none"> <li>Occupational ultraviolet light exposure is a risk factor for squamous cell carcinoma development</li> </ul>		✓
<b>Prevention</b> <ul style="list-style-type: none"> <li>Prolonged, regular sunscreen use may reduce melanoma incidence in white skinned people in Australia but it is difficult to extrapolate the data to the UK as there is a greater level of chronic UV exposure in Australia compared to the episodic nature of UV exposure in the UK</li> <li>Chemoprevention of nonmelanoma skin cancers cannot yet be broadly recommended</li> <li>Neither selenium nor antioxidant supplements should be recommended for cancer prevention based on current evidence</li> </ul>	✓	✓ ✓
<b>Investigation, diagnosis and staging</b> <ul style="list-style-type: none"> <li>Canine scent detection of melanoma, and related work into 'electronic noses', has potential for future diagnostic techniques</li> <li>Ultrasonography is superior to other imaging modalities in detecting regional lymph node metastases, and positron emission tomography-computed tomography (PET-CT) is superior to CT for distant metastases</li> </ul>	✓	✓
<b>Pharmacological management (non-melanoma)</b> <ul style="list-style-type: none"> <li>Cutaneous squamous cell carcinoma management has a distinct lack of randomised controlled trial data which needs to be urgently addressed by primary research</li> </ul>		✓
<b>Pharmacological management (melanoma)</b> <ul style="list-style-type: none"> <li>Adjuvant interferon alpha should not be offered as standard therapy to patients with melanoma, rather they should continue to be entered into clinical trials looking at new and emerging alternative adjuvant therapies</li> </ul>		✓
<b>Surgical management</b> <ul style="list-style-type: none"> <li>The revolving-door flap procedure should be the first choice for anterior auricular conchal defect reconstruction following wider skin tumour excision</li> <li>The efficacy of early completion lymph node dissection (CLND) vs delayed CLND in cutaneous melanoma is uncertain based on current evidence</li> <li>Recommendations on excision margins in primary melanoma should not be changed as current evidence is not convincing enough</li> </ul>	✓	✓ ✓

# 1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided. 'NICE cancer service guidance' refers to the clinical guideline stated in the introduction.

## 1.1 Organisation of skin cancer services

### GP-led melanoma follow-up

A randomised controlled trial (RCT) by [Murchie et al. \(2010\)](#) examining GP-led melanoma follow-up compared with traditional hospital follow-up in 142 patients, found that GP follow-up provides greater patient satisfaction (5 out of 15 aspects of patient satisfaction were improved in those followed up by GP; all  $p \leq 0.01$ ) without compromising the health status, anxiety or depression level of patients.

The results are interesting but weakened by some aspects of the study design. These include its small size, its short duration, a greater distance between patients and the hospital in the intervention group, and the possible increased motivation of participating GPs which may reduce external validity of the results to the wider GP population.

The follow-up arrangements used in the trial (up to 10 years) do not match the latest guidance from the British Association of Dermatologists (BAD) recommending between 1 and 5 years follow-up ([Marsden et al. 2010](#)).

The study did not look at costs, but [Coast et al. \(2005\)](#) have previously determined that a specialist dermatology service provided by a GP was in fact more expensive than hospital follow-up.

The [NICE cancer service guidance](#) does allow for the provision of community skin cancer services based at GP surgeries, for example in the management of low-risk basal cell carcinomas when specific circumstances have been met, and BAD guidelines ([Marsden et al. 2010](#)) suggest melanoma follow-up can be shared with primary care. In summary, despite greater patient satisfaction, the evidence here is not robust enough to fully recommend GP follow-up for the safe follow-up of people with melanoma.

#### Key reference

[Murchie P, Nicolson MC, Hannaford PC \(2010\) Patient satisfaction with GP-led melanoma follow-up: a randomised controlled trial. Br J Cancer 102: 1447–55](#)  
Full text: [www.nature.com/bjc/journal/v102/n10/full/6605638a.html](http://www.nature.com/bjc/journal/v102/n10/full/6605638a.html)

#### Supporting reference

[Coast J, Noble S, Noble A et al. \(2005\) Economic evaluation of a general practitioner with special interests led dermatology service in primary care. BMJ 33:1444–9](#)  
Full text: [www.bmj.com/content/331/7530/1444.full](http://www.bmj.com/content/331/7530/1444.full)

## 1.2 Risk factors

### Occupational UV exposure and squamous cell carcinoma risk

A systematic review and meta-analysis of 18 observational studies by [Schmitt et al. \(2011\)](#) found evidence for a consistent association between occupational ultraviolet (UV) light exposure and risk of squamous cell carcinoma (SCC) (pooled odds ratio = 1.77; 95% confidence interval [CI] 1.40 to 2.22).

Although there were elements of potential retrieval bias (only articles with abstracts from PubMed were included) and recall bias (concerns around assessing UV exposure in elderly patients via questionnaires, and questionnaires when used differed between studies), this is useful epidemiological research which has managed to isolate occupation from the confounders of recreational exposure, age and skin type, associating it directly with elevated SCC risk.

There are no management implications for the [NICE cancer service guidance](#), although this evidence may be of use to enhance any messages given to patients around risk factors for development of SCC.

Other relevant guidance includes 'Skin cancer prevention: information, resources and environmental changes' ([NICE public health guidance 32](#)) which encourages employers to conduct risk assessments and adopt policies to protect outdoor workers (referring them to the Health and Safety Executive for more details on developing policies), all of which are strengthened by the evidence from this review.

#### Key reference

Schmitt J, Seidler A, Diepgen TL (2011) Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis. *Br J Dermatol* 164: 291–307

Abstract: [www.onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.2010.10118.x/abstract](http://www.onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.2010.10118.x/abstract)

## 1.3 Prevention

### Sunscreen use and melanoma

In a follow up of their 1999 randomised controlled trial showing SCC to be preventable in the general population of Australia following daily sunscreen use, [Green et al. \(2011\)](#) revisited this study group of 1621 patients and performed a secondary analysis on melanoma prevention by regular sunscreen use.

The study from Queensland, Australia is currently the only RCT that has examined prevention of skin cancer by sunscreen in the general population. Participants from the original study were followed-up for a further 10 years and those assigned to daily sunscreen had significantly fewer new primary melanomas (11 vs 22 melanomas; hazard ratio [HR] = 0.5; 95% CI 0.24 to 1.02;  $p = 0.051$ ) and substantially fewer invasive melanomas (3 vs 11 melanomas; HR = 0.73; 95% CI 0.29 to 1.81).

The results should be interpreted with some caution as the study's primary endpoint was not melanoma, and invasiveness was looked at as an exploratory sub-group analysis. There are also concerns over external validity of these data to the UK as UV levels in Australia are considerably higher, leading to a greater degree of chronic UV exposure compared with the more episodic nature of exposure to UV in the UK, creating different skin cancer risk profiles in the two countries. In fact it may be that in the UK, the benefits of daily sunscreen use could be offset by inhibiting vitamin D production which may be protective against melanoma ([Newton-Bishop et al. 2011](#)).

The study provides useful evidence of potential melanoma prevention by sunscreen, however due to very different environmental factors in Australia, *daily* sunscreen use for white-skinned people in the UK as opposed to occasional use (such as on holidays) should be approached with caution.

The [NICE cancer service guidance](#) makes no direct recommendations on preventive measures, but recent guidance 'Skin cancer prevention: information, resources and environmental changes' ([NICE public health guidance 32](#)) sets out current skin cancer prevention advice. With new studies now showing significant links between sunscreen use and melanoma protection, and outdoor occupations and SCC risk, it is important that guidance is kept up-to-date with the latest emerging evidence.

#### Key reference

Green AC, Williams GM, Logan V et al. (2010) Reduced melanoma after regular sunscreen use: randomized trial follow-up. *Journal of Clinical Oncology* 29: 257–263  
Abstract: [www.jco.ascopubs.org/content/29/3/257.abstract](http://www.jco.ascopubs.org/content/29/3/257.abstract)

#### Supporting reference

Newton-Bishop JA, Chang YM, Elliott F et al. (2011) Relationship between sun exposure and melanoma risk for tumours in different body sites in a large case-control study in a temperate climate. *Eur J Cancer* 47: 732–41.  
Abstract: [www.ejancer.info/article/S0959-8049\(10\)00993-7/abstract](http://www.ejancer.info/article/S0959-8049(10)00993-7/abstract)

## Chemoprevention of nonmelanoma skin cancer

Two recent RCTs investigated chemoprevention in nonmelanoma skin cancer (NMSC); [Bailey et al. \(2010\)](#) using alfa-difluoromethylornithine (DFMO; an ornithine decarboxylase inhibitor) and [Elmets et al. \(2010\)](#) using celecoxib (a cyclooxygenase 2 [COX-2] inhibitor).

The RCT by Bailey et al. (2010) is the first to assess DFMO for prevention of NMSC, and found that in 291 patients with previous history of skin cancer, the primary endpoint (number of new NMSCs) did not differ significantly between DFMO and placebo groups after a mean of 4 years of treatment (260 vs 363 cancers;  $p = 0.069$ , two-sample  $t$  test). However further analysis showed that there were significantly fewer new basal cell carcinomas (BCC) in the DFMO compared with placebo group (163 vs 243 cancers; event rate 0.28 vs 0.40 BCC/person/year;  $p = 0.03$ ).

Trial limitations included not disclosing details of randomisation, not providing enough information about participants such as sunlight exposure and location of previous cancers, and not fully accounting for all randomised patients at the study end. There was also an imbalance in the mean number of prior cancers between treatment groups (4.23 DFMO group vs 4.91 placebo group) which may have affected results.

Although there was no conclusive result with NMSCs, the success with BCCs could indicate an area for future research.

The RCT by Elmets et al. (2010) found that in 240 patients with extensive actinic damage at high risk of developing NMSCs, incidence of actinic keratoses was no different between the celecoxib and placebo groups 9 months after randomisation, but at 11 months after randomisation and adjusting for age, sex, skin type, skin cancer history and time on study, there were significantly fewer NMSCs in the celecoxib than in the placebo group (RR = 0.41; 95% CI 0.23 to 0.72;  $p = 0.002$ ).

No information about blinding was provided, so selection and detection bias could not be ruled out. External validation is also at question, namely whether the effect would be seen in people with less extensive keratoses than those enrolled in this study.



The main concerns emerging from this trial however were safety issues with the drug. Although the length of follow-up and limited number of patients may not have been able to demonstrate a full cardiovascular adverse events profile in this study, the trial was in fact stopped by the FDA following adverse events with a different COX-2 inhibitor (rofecoxib) in another study. Safety concerns with celecoxib have also been highlighted elsewhere ([Bertagnolli et al. 2009](#)). None-the-less, the findings are of interest biologically and should encourage further studies with similar drugs but with improved safety profiles.

A further issue with both the Bailey et al. (2010) and Elmets et al. (2010) RCTs was the use of the term 'NMSC'. Amalgamating both SCC and BCC into this single endpoint could produce misleading results, for example if either SCC or BCC is particularly responsive to the intervention it may disguise a lack of effect in the other.

The current evidence is not substantial enough to modify current clinical practice (no direct recommendations around prevention are currently made in the [NICE cancer service guidance](#)). However, this is an interesting area with potential benefits for high-risk groups such as transplant patients or those with xeroderma pigmentosum, for whom preventative measures are important. Administration of chemopreventive agents may be ethically justified in these populations if sufficient evidence arose from future studies in which appropriate primary endpoints are investigated and adverse events closely monitored.

#### Key references

Bailey HH, Kim K, Verma AK et al. (2010) A randomized, double-blind, placebo-controlled phase 3 skin cancer prevention study of {alpha}-difluoromethylornithine in subjects with previous history of skin cancer. *Cancer Prev Res* 3: 35–47

Full text: [www.cancerpreventionresearch.aacrjournals.org/content/3/1/35.full](http://www.cancerpreventionresearch.aacrjournals.org/content/3/1/35.full)

Elmets CA, Viner JL, Pentland AP et al. (2010) Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. *JNCI: Journal of the National Cancer Institute* 102:1835–44

Full text: [www.jnci.oxfordjournals.org/content/early/2010/11/29/jnci.djq442.full](http://www.jnci.oxfordjournals.org/content/early/2010/11/29/jnci.djq442.full)

#### Supporting reference

Bertagnolli MM, Eagle CJ, Zauber AG et al. (2009) Five-year efficacy and safety analysis of the Adenoma Prevention with Celecoxib Trial. *Cancer Prev Res* 2:310–21

Full text: [www.cancerpreventionresearch.aacrjournals.org/content/2/4/310.full](http://www.cancerpreventionresearch.aacrjournals.org/content/2/4/310.full)

## Selenium and antioxidant supplements in skin cancer prevention

Two further papers relating to skin cancer prevention were also identified for the Evidence Update. In a Cochrane systematic review of 49 prospective observational studies and six RCTs, [Dennert et al. \(2011\)](#) looked at the anti-cancer potential of selenium. It was found that selenium exposure was associated with a reduced overall cancer incidence (summary OR = 0.69; 95% CI 0.53 to 0.91) and mortality (OR 0.55, 95% CI 0.36 to 0.83). However these conclusions are limited by issues with study design and quality of data, and in fact some of the most reliable results from the RCTs indicated that organic selenium actually *increased* the risk of nonmelanoma skin cancer. This evidence therefore has no implications for the [NICE cancer service guidance](#).

In a follow up to their 7.5 year RCT of 12,741 participants (which indicated antioxidant supplements led to a significantly increased risk of total skin cancers and melanoma in women, but made no difference to risk in men) [Ezzedine et al. \(2010\)](#) investigated residual or delayed effects of the supplementation 5 years after the initial intervention. Among women, post-intervention appearance of 10 melanomas (9 in men), 6 SCCs (15 in men) and 40 BCCs (36 in men) were reported, but there was no observed increase in melanoma risk once supplementation had ended. There were no delayed effects on melanoma or nonmelanoma

skin cancers for either sex. The study was reasonably well conducted, with enough data presented to suggest a low risk of attrition and detection bias.

The authors concluded that the observed decline in skin cancer risk among women who had stopped supplementation suggests that antioxidants may have a role in skin cancer causation. The authors further recommended that routine antioxidant therapy should be avoided in high-risk individuals. The findings should be interpreted with caution due to limitations of low numbers of events in subgroups, and potential confounding by voluntary intake of antioxidants post-intervention.

#### Key references

Dennert G, Zwahlen M, Brinkman M et al. (2011) Selenium for preventing cancer. *Cochrane Database of Systematic Reviews* issue 5: CD005195

Full text: [www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005195.pub2/pdf](http://www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD005195.pub2/pdf)

Ezzedine K, Latreille J, Kesse-Guyot E et al. (2010) Incidence of skin cancers during 5-year follow-up after stopping antioxidant vitamins and mineral supplementation. *Eur J Cancer* 46: 3316–22

Abstract: [www.ejancer.info/article/S0959-8049\(10\)00483-1/abstract](http://www.ejancer.info/article/S0959-8049(10)00483-1/abstract)

## 1.4 Investigation, diagnosis and staging

### Canine scent detection of cancer

In a systematic review, [Moser and McCulloch \(2010\)](#) brought together a number of studies into canine scent detection of human cancers. This is an emerging field and one which has been gathering pace in recent years. Detection of melanoma by dogs has now been reported, alongside breast, bladder, lung and ovarian cancers, with varying success rates. The included studies (six observational studies, one of which studied 89 melanoma patients) are of mixed quality but if some of the more compelling research can be repeated (for example, 99% specificity and sensitivity in lung cancer detection using exhaled breath) then using trained dogs to diagnose some forms of cancer may be a possibility. Ongoing research building upon the work done in this field is currently investigating the potential of 'electronic noses' in diagnosis of human cancers ([Hakim et al. 2011](#)).

Although limited in its implications for current clinical practice and the [NICE cancer service guidance](#), the review contains a useful analysis of methodological issues such as the training procedures used with the sniffer dogs, which may be of value to planning and designing future research in this field.

#### Key reference

Moser E, McCulloch M (2010) Canine scent detection of human cancers: A review of methods and accuracy. *Journal of Veterinary Behaviour: Clinical Applications and Research* 5: 145–52

Abstract: [www.worldwidescience.org/topicpages/c/canine+scent+detection.html](http://www.worldwidescience.org/topicpages/c/canine+scent+detection.html)

#### Supporting reference

Hakim M, Billan S, Tisch U et al. (2011) Diagnosis of head-and-neck cancer from exhaled breath. *Br J Cancer* 104:1649–55.

Abstract: [www.nature.com/bjc/journal/v104/n10/full/bjc2011128a.html](http://www.nature.com/bjc/journal/v104/n10/full/bjc2011128a.html)

## Diagnostic imaging of melanoma

In a substantial meta-analysis of 74 studies of 10,528 patients, [Xing et al. \(2011\)](#) investigated diagnostic imaging in melanoma patients. This is a thorough systematic review of the literature, although as the included studies cover a period of almost 20 years, diagnostic criteria and imaging quality varied between studies, and also most studies had a retrospective design.

The analysis concluded that ultrasonography was superior in detecting regional lymph node metastases, and positron emission tomography-computed tomography (PET-CT) was superior to CT in detecting distant metastases, both for the staging and surveillance of melanoma.

The evidence within this paper reinforces previous messages from the most recent [Annual Evidence Update for skin cancer \(NHS Evidence 2010\)](#), describing greater success of 18-fluorodeoxyglucose (18-FDG) PET in detecting distant metastases compared with its lesser ability to detect regional metastases.

This evidence is of importance for commissioning and investment in both ultrasound and PET-CT. Access to PET-CT and ultrasound will vary around the UK; recent initiatives have helped to increase access to PET-CT, but specialised ultrasound availability may be more variable with local differences such as the number of trained ultrasonographers potentially affecting waiting times. It is, however, important to have adequate access to *both* imaging modalities. As the detection of early recurrent disease is likely to become increasingly important with the emergence of treatments that may soon be able to provide benefits for asymptomatic disease, the need to assign patients (particularly those at high risk) to the most appropriate imaging modality is a key clinical consideration.

The [NICE cancer service guidance](#) makes no direct recommendations around imaging of melanoma, and current BAD guidance for managing cutaneous melanoma ([Marsden et al. 2010](#)) states there is no definitive routine indication for imaging. This systematic review suggests that both guidance documents need to be updated accordingly. This is a rapidly moving field which will require future reviews to keep pace with further technological advances.

### Key reference

Xing Y, Bronstein Y, Ross MI et al. (2011) Contemporary Diagnostic Imaging Modalities for the Staging and Surveillance of Melanoma Patients: a Meta-analysis. *JNCI: Journal of the National Cancer Institute* 103:129–42

Abstract: [www.jnci.oxfordjournals.org/content/103/2/129.short](http://www.jnci.oxfordjournals.org/content/103/2/129.short)

### Supporting reference

2010 Annual Evidence Update on Skin Cancer (NHS Evidence).

Full text: [www.arms.evidence.nhs.uk/resources/hub/35871/attachment](http://www.arms.evidence.nhs.uk/resources/hub/35871/attachment)

## 1.5 Pharmacological management (non-melanoma)

### Interventions for non-metastatic SCC of the skin.

A Cochrane systematic review by [Lansbury et al. \(2010\)](#) examined data from RCTs of non-metastatic SCC of the skin. The review uncovered only one RCT of 65 patients looking at a relatively obscure area of therapy comparing adjuvant 13-cis-retinoic acid and interferon alpha after surgery with or without radiation treatment, with no adjuvant therapy after initial treatment. No difference in time to tumour recurrence was found between the groups in this RCT.

This review highlights a considerable and surprising paucity of data in the form of RCTs for the management of cutaneous SCC, which is the second most common skin cancer and is becoming increasingly common worldwide. Research to confirm the most appropriate provision of, for example, radiotherapy and surgical treatments to different patient groups would be of significant interest.

Further work is now being pursued on the basis of these review findings, including [a second review by Lansbury et al.](#) of SCC management looking at observational studies, given the lack of robust data in the form of RCTs.

No implications for current practice or the [NICE cancer service guidance](#) can be taken from this lack of evidence, and there is a clear and urgent need for well-designed clinical trials in this area.

#### Key reference

Lansbury L, Leonardi-Bee J, Perkins W et al. (2010) Interventions for non-metastatic squamous cell carcinoma of the skin. *Cochrane Database of Systematic Reviews* issue 4: CD007869  
Full text: [www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD007869.pub2/pdf/standard](http://www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD007869.pub2/pdf/standard)

#### Supporting reference

Lansbury L, Bath-Hextall F, Leonardi-Bee J et al. Effectiveness of interventions for primary, non-metastatic squamous cell carcinoma of the skin: a systematic review of observational studies. *PROSPERO* 2011:CRD42011001450. Available from [www.crd.york.ac.uk/PROSPERO/full\\_doc.asp?ID=CRD42011001450](http://www.crd.york.ac.uk/PROSPERO/full_doc.asp?ID=CRD42011001450)

## 1.6 Pharmacological management (melanoma)

### Adjuvant interferon alpha

Three recent studies have examined the effect of adjuvant interferon alpha (IFN-alpha) in patients with melanoma.

In a systematic review and meta-analysis, [Mocellin et al. \(2010\)](#) compiled data from 14 RCTs of 8122 patients with high-risk melanoma and for the first time were able to show a statistically significant improvement amongst patients treated with adjuvant IFN-alpha not only in disease-free survival (HR for disease recurrence = 0.82; 95% CI 0.77 to 0.87;  $p < 0.001$ ) but also in overall survival (HR for death = 0.89; 95% CI 0.83 to 0.96;  $p = 0.002$ ).

Although the included studies used many different doses and preparations, the review was well designed and provides useful evidence for the efficacy of IFN-alpha adjuvant therapy. However it appears that the effect on overall survival is only seen upon combining data from thousands of patients; individual RCTs do not seem to show a similar effect in isolation (the trials in this meta-analysis were also limited by inadequate reporting). Combined with the considerable toxicity of the drug and alongside its high cost, the uncertainty of treatment efficacy at an individual patient level means that this evidence is unlikely to affect current clinical practice.

IFN-alpha is not used in standard UK clinical practice, in line with the [NICE cancer service guidance](#) which states that patients should only receive IFN-alpha therapy as part of a clinical trial, and BAD guidelines ([Marsden et al. 2010](#)) also suggest that patients should be entered into melanoma adjuvant trials rather than receive interferon as standard therapy. Trials with bevacizumab and ipilimumab are two of those currently ongoing in the UK at the present time.

In order for these high cost and high toxicity adjuvant drugs to be established as standard treatments in future, routine collection and storage of biological samples from all patients (with appropriate consent) should be established during RCTs to aid in the discovery of biomarkers predictive of treatment benefit.

Two RCTs by [Hansson et al. 2011](#) (855 patients) and [Hauschild et al. 2011](#) (850 patients) also investigated intermediate-dose and low-dose IFN-alpha respectively in patients with melanoma. Although good trials, neither was able to demonstrate significantly improved overall survival following adjuvant IFN-alpha, and they now add further weight to the literature which has informed the reduction in interferon use in the UK in recent years.

#### Key references

Hansson J, Aamdal S, Bastholt L et al. (2011) Two different durations of adjuvant therapy with intermediate-dose interferon alfa-2b in patients with high-risk melanoma (Nordic IFN trial): a randomised phase 3 trial. *Lancet Oncology* 12: 144–52  
Abstract: [www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(10\)70288-6/abstract](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(10)70288-6/abstract)

Hauschild A, Weichenthal M, Rass K et al. (2010) Efficacy of low-dose interferon {alpha}2a 18 versus 60 months of treatment in patients with primary melanoma of  $\geq 1.5$  mm tumor thickness: results of a randomized phase III DeCOG trial. *J Clin Oncol* 28: 841–6  
Full text: [www.jco.ascopubs.org/content/28/5/841.full.pdf](http://www.jco.ascopubs.org/content/28/5/841.full.pdf)

Mocellin S, Pasquali S, Rossi CR et al. (2010) Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. *J Natl Cancer Inst* 102: 493–501  
Full text: [www.jnci.oxfordjournals.org/content/102/7/493.full.pdf](http://www.jnci.oxfordjournals.org/content/102/7/493.full.pdf)

### **Ipilimumab for metastatic melanoma**

An RCT of ipilimumab therapy in patients with previously treated metastatic melanoma conducted by [Hodi et al. \(2010\)](#) demonstrated improved overall survival in 403 patients in the treatment arm (ipilimumab plus a glycoprotein peptide vaccine) compared with 136 patients randomised to receive the glycoprotein vaccine alone (10.0 months [95% CI 8.5 to 11.5] vs 6.4 months [95% CI 5.5 to 8.7]; HR for death = 0.68;  $p < 0.001$ ). A further group of 137 patients received ipilimumab alone (median overall survival 10.1 months).

Although a well-conducted study, the interventions are of concern as the control was neither a placebo nor the more widely acknowledged dacarbazine comparator. Instead an experimental peptide vaccine was used raising questions as to whether patients who received the vaccine did worse than if they had received no active treatment. The trial also revealed notable morbidity possibly related to ipilimumab treatment, including 12 treatment-related deaths in the ipilimumab arms (compared with 2 treatment-related deaths in the glycoprotein vaccine group).

[Robert et al. \(2011\)](#) have also published work on ipilimumab, and their more recent RCT found that in 250 patients with previously untreated metastatic melanoma receiving ipilimumab plus dacarbazine, there was a modest but statistically significant overall survival benefit compared with 252 patients receiving dacarbazine plus placebo (11.2 months [95% CI 9.4 to 13.6] vs 9.1 months [95% CI 7.8 to 10.5], with more encouraging higher survival rates at 1, 2 and 3 years in the ipilimumab plus dacarbazine group; HR for death = 0.72;  $p < 0.001$ ). Although there were no deaths attributable to treatment in the ipilimumab plus dacarbazine group, there was still a considerable number of grade 3 or 4 adverse events. The trial was well conducted, however there were minor issues including a lack of details for the randomisation method, concealment of allocation and blinding of investigators to other important confounders.

A NICE technology appraisal of ipilimumab is currently in progress. A preliminary decision is expected very soon ([www.guidance.nice.org.uk/TA/WaveCRS2/48](http://www.guidance.nice.org.uk/TA/WaveCRS2/48)) and the final guidance is anticipated in early 2012. The appraisal will review the available evidence related to this treatment and establish relative cost effectiveness. This new guidance should be referred to as soon as it is published.

### Key references

Hodi FS, O'Day SJ, McDermott DF et al. (2010) Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 363: 711–23  
Full text: [www.nejm.org/doi/pdf/10.1056/NEJMoa1003466](http://www.nejm.org/doi/pdf/10.1056/NEJMoa1003466)

Robert C, Thomas L, Bondarenko I et al. (2011) Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma. *N Engl J Med* 364: 2517–2526  
Full text: [www.nejm.org/doi/full/10.1056/NEJMoa1104621](http://www.nejm.org/doi/full/10.1056/NEJMoa1104621)

## Vemurafenib for metastatic melanoma

[Chapman et al. \(2011\)](#) conducted the first RCT to investigate vemurafenib in patients with previously untreated metastatic melanoma with the BRAF V600E mutation. In this study of 675 patients, those receiving vemurafenib had a greater overall survival at 6 months than those receiving dacarbazine (84% [95% CI 78 to 89] vs 64% [95% CI 56 to 73]). Benefits were also seen with vemurafenib in the interim analysis for overall survival and the final analysis for progression-free survival (relative reductions in risk of death [63%] and risk of death or disease progression [74%] compared with dacarbazine;  $p < 0.001$ ).

Vemurafenib only works in melanomas with the identified BRAF mutation (around half of tumours) which means that although the treatment is specific, not all patients can be offered the therapy.

The trial had some minor issues with potential for bias (information not given about concealment of allocation, whether groups were followed up for the same length of time, whether investigators were blind to the treatment or other confounders, and industry sponsorship) but otherwise was well designed and adverse events were within acceptable bounds.

The treatment is not yet licensed in the UK. The preliminary stages of a NICE technology appraisal are underway to review all available evidence related to this treatment and establish relative cost effectiveness.

### Key reference

Chapman PB, Hauschild A, Robert C et al. (2011) Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. *N Engl J Med* 364: 2507–2516  
Full text: [www.nejm.org/doi/full/10.1056/NEJMoa1103782](http://www.nejm.org/doi/full/10.1056/NEJMoa1103782)

## 1.7 Surgical management

### Ear reconstruction following wide tumour excision

In an RCT [Dessy et al. \(2010\)](#) compared two well-known methods of ear reconstruction following wide tumour excision in 40 patients with BCC or SCC (stage T1 or T2) or melanoma (T1). Patients randomised to the revolving-door (RD) flap procedure demonstrated superior cosmetic outcome and colour and texture matching than those who received full-thickness skin grafts (Wilcoxon matched-pairs rank-sum test;  $p < 0.0001$ ). However a lack of details about the comparison groups and the care they received means performance bias cannot be ruled out.

This trial confirms what many UK plastic surgeons already practice, namely RD flap should be the first choice for anterior auricular conchal defect reconstruction following wider skin tumour excision. The [NICE cancer service guidance](#) does not currently provide specific recommendations within this field.



### Key reference

Dessy LA, Figus A, Fioramonti P et al. (2010) Reconstruction of anterior auricular conchal defect after malignancy excision: revolving-door flap versus full-thickness skin graft. *J Plast Reconstr Aesthet Surg* 63: 746–52

Abstract: [www.jprasurg.com/article/S1748-6815\(09\)00203-4/abstract](http://www.jprasurg.com/article/S1748-6815(09)00203-4/abstract)

## Early vs delayed completion lymph node dissection

[Faries et al. \(2010\)](#) looked again at data from the previously reported randomised Multicenter Selective Lymphadenectomy Trial I (MSLT-I) to compare the effect on morbidity of immediate completion lymph node dissection ('early CLND'; performed following detection of metastasis by sentinel lymph node biopsy) versus therapeutic dissection ('delayed CLND'; performed following clinical recurrence) in a subgroup of 357 patients with cutaneous melanoma.

Although there was no difference in morbidity between the groups, lymphoedema was found to be higher in the delayed CLND group (20.4% vs 12.4%;  $p = 0.04$ ). However the results should be interpreted cautiously as the comparison could potentially be seen as invalid; patients receiving early CLND by definition have less advanced disease than those receiving delayed CLND, which is a major confounder in lymphoedema risk. The trial also did not report enough data to rule out attrition and detection bias (concerns with loss of participants, and investigators knowledge of which intervention was given).

This evidence has no impact upon the [NICE cancer service guidance](#), and the questions posed within the trial will not be adequately addressed until a further RCT such as MSLT-II reports.

[Pasquali et al. \(2010\)](#) similarly compared early and delayed CLND in cutaneous melanoma in both a retrospective non-randomised case series of 190 patients, and a meta-analysis of 5 other non-randomised studies plus the case series conducted for this paper (2633 patients in total). Although the case series found no difference in 5-year overall survival following early and delayed CLND, the meta-analysis showed a higher risk of death following late CLND compared with early CLND (HR = 1.60; 95% CI 1.28 to 2.00;  $p < 0.0001$ ). However the implications of these results are limited by the non-randomised nature of the included studies, and in fact these data have now largely been superseded by the randomised MSLT-I trial described above and so have no impact on the [NICE cancer service guidance](#).

### Key references

Faries MB, Thompson JF, Cochran A et al. (2010) The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the Multicenter Selective Lymphadenectomy Trial (I). *Ann Surg Oncol* 17: 3324–9

Abstract: [www.springerlink.com/content/m261t24336wm3210/](http://www.springerlink.com/content/m261t24336wm3210/)

Pasquali S, Mocellin S, Campana LG et al. (2010) Early (sentinel lymph node biopsy-guided) versus delayed lymphadenectomy in melanoma patients with lymph node metastases : personal experience and literature meta-analysis. *Cancer* 116: 1201–9

Full text: [www.onlinelibrary.wiley.com/doi/10.1002/cncr.24852/full](http://www.onlinelibrary.wiley.com/doi/10.1002/cncr.24852/full)

## Excision margins in primary melanoma

In a systematic review and meta-analysis of five RCTs comprising 3295 patients, [Mocellin et al. \(2010\)](#) re-examined wide (3–5 cm) versus narrow (1–2 cm) excision margins in primary melanoma. The results tentatively suggest that narrow excision margins are less safe, however a number of limitations to the investigation, including a lack of data reporting in some of the RCTs, a non-homogenous study design between the RCTs, and the small number of included trials, meant definitive conclusions could not be drawn.

The [NICE cancer service guidance](#) provides no direct recommendations for excision margins, however BAD guidelines ([Marsden et al. 2010](#)) suggest margins of between 1–3 cm corresponding to tumour thickness across the range <1 mm to >4 mm. Although this review questions the stance that narrower margins are as safe as wide margins, the evidence is not convincing enough to change current practice or guidelines.

### Key reference

Mocellin S, Pasquali S, Nitti D (2011) The impact of surgery on survival of patients with cutaneous melanoma: revisiting the role of primary tumor excision margins. *Ann Surg* 253:238–43  
Abstract: [www.ncbi.nlm.nih.gov/pubmed/21173691](http://www.ncbi.nlm.nih.gov/pubmed/21173691)



## 2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

- **GP-led melanoma follow-up for improved patient satisfaction**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411254](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411254)
- **Increased sunscreen use to reduce incidences of skin cancer**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411120](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411120)
- **Canine scent detection methods for early diagnosis of human cancers**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411172](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411172)
- **Ultrasonography or PET-CT in the staging and surveillance of melanoma patients**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411255](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411255)
- **Interferon Alpha adjuvant therapy in patients with high-risk melanoma**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411173](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411173)
- **Narrow excision margins versus wide excision margins on disease-specific survival of patients with primary cutaneous melanoma**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411174](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411174)
- **Early (sentinel lymph node biopsy-guided) versus delayed lymphadenectomy in melanoma patients with lymph node metastases**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411175](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411175)

Two other uncertainties were identified from sources of evidence that, following critical appraisal, were not selected for inclusion in the final evidence update:

- **Behavioural counselling to reduce incidences of skin cancer**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411119](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411119)
- **Sun-protective behaviours and reduced Vitamin D levels, with increases in diseases hypothesised to be affected by Vitamin D**  
[www.library.nhs.uk/duets/ViewResource.aspx?resID=411121](http://www.library.nhs.uk/duets/ViewResource.aspx?resID=411121)

Further evidence uncertainties for skin cancer can be found at [www.library.nhs.uk/duets/](http://www.library.nhs.uk/duets/). DUETs has been established in the UK to publish uncertainties about the effects of treatment which cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

# Appendix A: Methodology

## Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance (2006; partially updated 2010). Available from [www.nice.org.uk/CSGSTIM](http://www.nice.org.uk/CSGSTIM)

On the advice of the Evidence Update Advisory Group chair, preventing skin cancer (other than public health prevention) was additionally included in the scope.

## Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 January 2010 (the end of the search period of the most recent Annual Evidence Update) to 15 June 2011:

- British Nursing Index
- CINAHL
- Cochrane Database of Systematic Reviews – Cochrane Library
- Embase
- MEDLINE
- PsycINFO

Table 1 provides details of the search strategy used. Two high-impact studies (Chapman et al. 2011 and Roberts et al. 2011) were also identified outside of the literature search (published subsequent to the search dates but prior to publication of the Evidence Update). Commentaries on these papers are included within this Evidence Update.

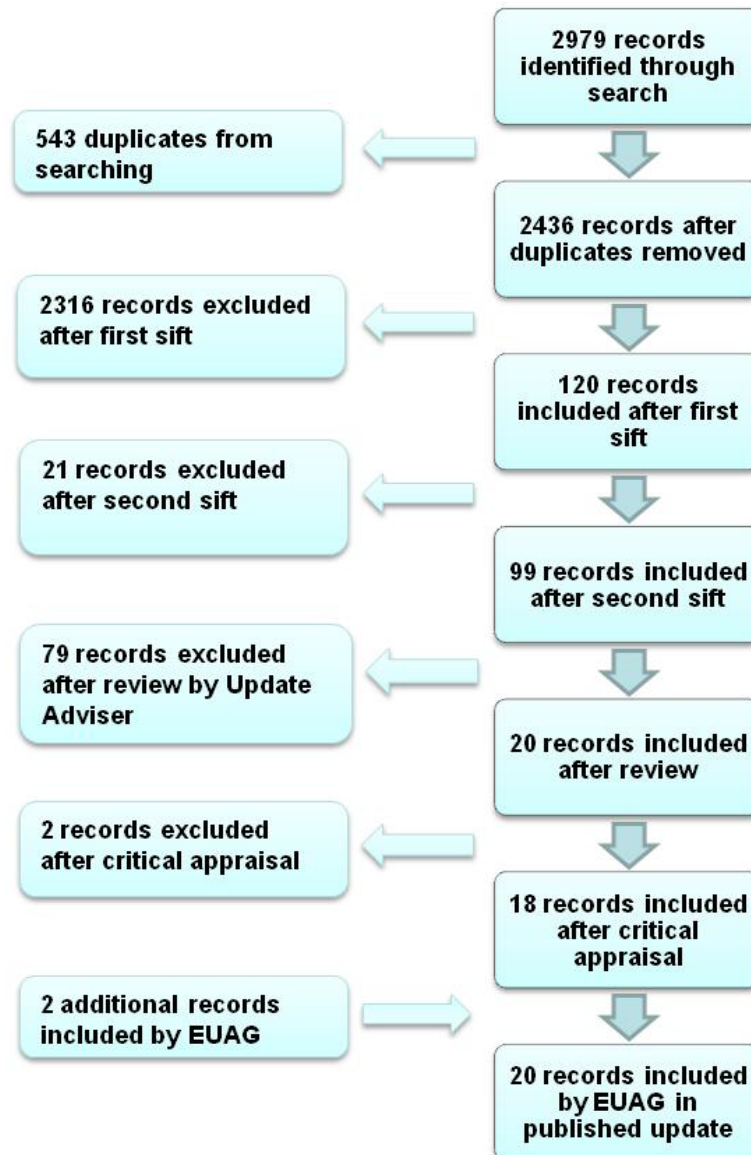
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the Evidence Update Advisory Group) is available on request from [contactus@evidence.nhs.uk](mailto:contactus@evidence.nhs.uk).

**Table 1 MEDLINE search strategy (adapted for individual databases)**

1	exp skin neoplasms/
2	exp melanoma/
3	exp carcinoma basal cell/
4	exp carcinoma squamous cell/
5	exp "Neoplasms, Adnexal and Skin Appendage"/
6	exp Carcinoma, Merkel Cell/
7	exp Lymphoma, T-Cell, Cutaneous/
8	sarcoma, kaposi/
9	exp Nevus/
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

Figure 1 Flow chart of the evidence selection process



# Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

## Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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