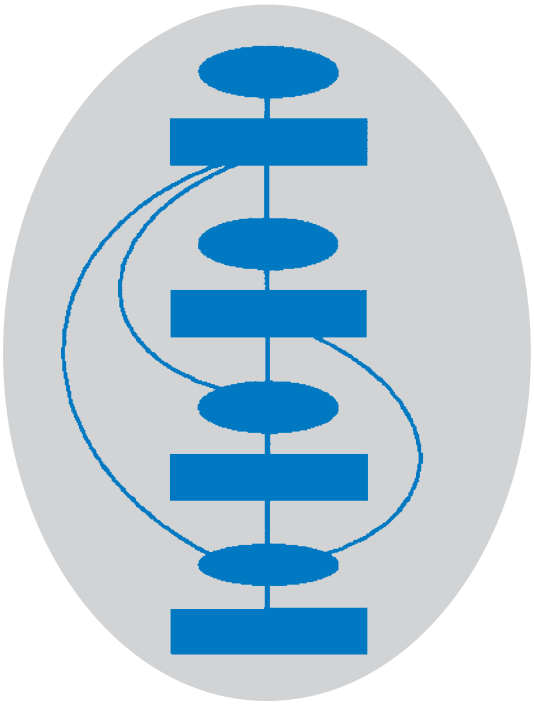
NHS

National Institute for Health and Clinical Excellence

Guidance on Cancer Services

Improving Outcomes for People with Sarcoma

The Evidence Review



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Evidence tables

Introduction

This review summarises the evidence appraised for the production of the recommendations in Guidance for Commissioning Cancer Services Improving Outcomes in Sarcoma: The Manual. Topic areas are presented in the same order as in the Manual.

The purpose of the evidence review is to determine the current evidence on interventions and models of care to improve service provision for the treatment of patients with sarcoma. Sarcoma is rare and presents in diverse anatomical sites leading to confusion over the appropriate place for diagnosis and treatment. Although it is apparent that people with sarcoma are treated in a variety of healthcare settings, comparing these models of care is difficult. There is the issue of publication bias towards larger centres. The rarity of sarcoma means there is a lack of studies originating in primary or secondary care, beyond occasional case reports. Most evidence is from case series in specialist tertiary or quaternary centres. Population based studies, potentially useful in comparing treatment settings, are few in sarcoma. The rarity of sarcoma also limits the statistical power of many studies.

Initiatives to improve health care services are often several steps removed from patients themselves and it is often hard to attribute cause and effect when comparing different service models in terms of patient outcomes. While it is difficult to predict the influence of intermediate factors, it is assumed that advances in health care service delivery and practice will result in improvements in patient outcomes.

Methodology

Searching for evidence

a) Research question development

The members of the Guidance Development Group (GDG) were asked to consider the issues covered in the project scope and to submit research questions covering these issues.

b) Literature searching

The NCC-C information specialist constructed search strategies to identify published evidence for the research questions set by the GDG. In most cases the main search strategy, provided in Appendix A, was combined with more specific terms to identify relevant studies. The literature searching period ended on the 3rd of February 2005. Relevant evidence submitted by GDG members or stakeholders after this date, however, was included.

The titles and abstracts of studies identified by the literature searches were initially screened for relevance by the information specialist and then by the NCC-C researcher. Copies of potentially relevant papers were then obtained for critical appraisal. Studies cited in these papers were also considered for inclusion if relevant. GDG members and stakeholders were also asked to submit relevant evidence.

Given the scarcity of evidence for many of the research questions, abstracts were included as evidence if their results were not published elsewhere, but were considered to have a high risk of bias. Similarly papers not in English or French were appraised on the basis of their English abstract if available, but again were considered to have a high risk of bias.

Synthesising evidence

Studies were critically appraised using the methodology from the NICE Guideline Development Methods manual (National Institute for Health and Clinical

Excellence 2005). Each study was graded using the NICE hierarchy of evidence and the quality checklists and relevant data were entered into an evidence table. The tables recommended for use in the NICE methodology manual were modified to accept the type of studies identified for service guidance. Owing to practical limitations the final selection of studies, critical appraisal and data extraction were undertaken by a single researcher. Evidence tables were circulated to the GDG members for comments. Finally the evidence for each research question was summarised in the form of a considered judgement form (modified from the Scottish Intercollegiate Guideline Network methodology).

The rarity of sarcoma and the focus of the research questions on service models meant there was almost no available evidence from randomised controlled trials.

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. Experts were identified by asking relevant registered stakeholders for a suitable nomination to deal with a particular topic area. Three position papers, on prosthetic rehabilitation of the post tumour amputee, the management of people with head or neck sarcoma and the management of gastro intestinal stromal tumours (GIST), were presented at the GDG meetings for discussion and are included as Appendices B and C.

Health economic evidence

Economic evidence was extracted from the evidence tables, where it existed 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.

Drafting and agreeing recommendations

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

Once an early draft of the guidance was produced, the GDG members were asked to review the draft document. Members were asked to consider whether the recommendations were justified from the evidence presented and whether they were sufficiently practical and precise to allow health service commissioners and the relevant front line healthcare professionals to implement them. The absence of high quality evidence for the majority of the research questions made the grading of the recommendations impractical.

Group support consultants from the University of Glamorgan assisted the GDG in a number of ways. An interactive group support system, which allowed anonymous polling of the group, was used during meetings to help the group reach consensus, to resolve conflicts and to vote for key recommendations. A questionnaire about the GDG members' feelings on the group process was issued after each meeting and the group support consultants provided feedback to the GDG Chairperson following each session on aspects of the group process.

Writing of the guidance

The Chair and Clinical Lead of the GDG coordinated the first formal draft version of the guidance 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.

Patient perspectives

The questions

a) What are the views of patients with cancer on travelling for specialist treatment or diagnosis?

b) In people with sarcoma, is there evidence for the effectiveness of psychosocial interventions?

c) What are the information needs of people with sarcoma?

Nature of the evidence

a) Patient travel

Data from 10 studies were extracted into an evidence table, including a systematic review on accessibility and centralisation in cancer services. Five observational studies of good to poor quality surveyed people for their views on travelling for cancer treatment. Four observational studies of good to poor quality reported indirect estimates of patients' views on travel, such as the uptake of treatment options requiring more or less travelling. Of the nine primary studies, patient travel was for radiotherapy in four cases, surgery in two cases and any treatment in three cases.

b) Psychosocial interventions

No studies designed to measure the effectiveness of psychosocial interventions for people with sarcoma were identified. Three small observational studies reported the views of people with sarcoma on the effectiveness of psychosocial interventions.

The NICE guidance on Improving Supportive and Palliative Care for Adults with Cancer contains a comprehensive review of the effectiveness of psychosocial interventions for people with cancer and this evidence was used for the recommendations.

c) Information needs

Evidence included five observational studies, all of poor quality, and two qualitative studies. Three studies surveyed patients for their information needs. One study reported a psychosocial intervention that included information on sarcoma. One study concerned the accuracy of internet information about sarcoma. The qualitative evidence was a review article and a patient's personal account.

Recommendations about the development and dissemination of patient information were informed by the generic evidence reviewed in The NICE guidance on Improving Supportive and Palliative Care for Adults with Cancer.

Summary of the supporting evidence for the recommendations

a) Patient travel

Patients are likely to face an increased burden of travel as a consequence of the recommendations for specialist treatment. A UK systematic review (Ferguson 1996) concluded that people with cancer would overcome such access difficulties in order to receive appropriate treatment. This view was supported by primary studies that surveyed patients for their views (Guidry *et al.* 1997; Barton *et al.* 2001; Fitch *et al.* 2003; Kearney 2003; Teenage Cancer Trust: unpublished data 2004). In these studies travelling for treatment was consistently seen as an inconvenience but people were prepared to travel if necessary.

There was less agreement, however, among studies of the uptake of treatment depending on travel time. The UK study of Cosford and co-workers (Cosford *et al.* 1997) reported that the uptake of radiotherapy did not appear to be influenced by travel time. A US study (Meden *et al.* 2002) found that women with breast cancer who opted for more radical surgery, which required less travelling, tended to live further from the treatment centre. Two other US studies (Wright *et al.* 1994; Finlayson *et al.* 1999) presented patients and healthcare workers with hypothetical treatment choices in order to estimate the additional risk of morbidity or mortality that would balance a reduction in travelling time or distance. A

minority of people were prepared to accept increased risk of morbidity or mortality in order to reduce travel time. The evidence suggests that, when confronted with different treatment options, travel time is a consideration in a person's choice of treatment.

b) Psychosocial interventions

People with sarcoma, in the observational study of Payne and co-workers (Payne *et al.* 1997), reported decreased negative feelings following an intervention which involved relaxation, group support and education. Similarly a peer support intervention, where people who had lost a limb due to sarcoma were visited by a fellow patient, was reported as beneficial by patients (May *et al.* 1979).

76% of respondents to the survey by the charity Sarcoma UK (Sarcoma UK: unpublished data 2004) found contact with other patients useful and 15% had attended a sarcoma support group. Some people, however, found contact with their peers difficult. Patients who received counselling said it was useful, although most of those offered counselling declined it.

The sarcoma specific evidence suggests patients report psychosocial interventions as beneficial. Stronger evidence reviewed in NICE guidance on Improving Supportive and Palliative Care in Adults with Cancer indicates such interventions are useful in the reduction of anxiety in people with cancer. There is insufficient evidence, however, to strongly recommend any specific psychosocial intervention in this patient group.

c) Information needs

Responses to the Sarcoma UK survey (Sarcoma UK: unpublished data 2004) suggested that general information about sarcoma is not routinely distributed to patients. Approximately half of the respondents to the Teenage Cancer Trust Survey (Teenage Cancer Trust: unpublished data 2004) said that the cancer information they received was not appropriate for someone their age. Seven percent of the survey's respondents had STS and 19% had bone cancer.

The evidence suggested a demand for websites with sarcoma information; between 46% and 69% of patients in two small UK studies (Rao 2003; Sarcoma UK: unpublished data 2004) said they would use the Internet as a source of information about sarcoma. Two studies examined the quality of sarcoma websites, in 1999 (Biermann *et al.* 1999) and 2003 (Rao 2003), and found a wide range in the quality of internet information about sarcoma, with some websites of poor quality.

Several themes relating to information needs were identified in qualitative reports (Fedora 1985; Kaiser 1988). Fear of the unknown was a source of anxiety for people with sarcoma. Detailed information about future tests, procedures and their expected outcomes could help to reduce this anxiety and include the patient in decision making. Medical staff should use cues from patients to judge their information requirements.

Table 1.a Patient travel

Abbreviations: STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Barton *et al.* (2001)	To identify and evaluate important patient-based outcomes that are specific to the palliative radiotherapy of bone metastases.	Cross sectional study.	74 patients with bone metastases treated with radiotherapy. AUSTRALIA	Patients' priorities in radiotherapy.	Although on average patients rated the travelling distance to the treatment centre as important, sustained pain relief and minimizing the risk of future complications were seen as the main priorities.	Some patients declined to participate because of deteriorating health, possible bias. Design of the questionnaire was based on a literature search and patient interviews. Inappropriate use of the mean with ordinal data.	4-
Cosford *et al.* (1997)	To examine whether longer travel times for radiotherapy are associated with reduced overall uptake of radiotherapy treatment, or with reduced uptake of palliative as opposed to radical radiotherapy.	Observational case series.	Residents of Bedfordshire and Hertfordshire registered by the Cancer Registries as attending hospital with a diagnosis of cancer, and registered as receiving radiotherapy treatment. UK	Radiotherapy uptake.	There was no significant correlation between travel times for treatment and overall radiotherapy uptake ($r = 0.40$, $p = 0.18$), or with the ratio of palliative to radical radiotherapy at a single centre ($r = –0.29$, $P = 0.34$). Both measures of uptake showed considerable variability. Longest travel times were about one hour. Authors concluded “Travel times up to one hour do not appear to reduce radiotherapy uptake, and the variability observed is likely to be due to other factors. The recommendation of the Chief Medical Officer's expert advisory group on cancers, that radiotherapy should be provided in larger cancer centres, is unlikely to result in lower radiotherapy uptake with travel times of this order."	Individual patient travel time was not measured. An average travel time to the cancer centre was estimated for each of the 14 districts (n=14 for correlation analysis). Radiotherapy uptake was calculated using Cancer Registry data as the proportion of total number of cancer patients receiving radiotherapy. This approach cannot estimate the true uptake of radiotherapy.	4-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Ferguson (1996)	To review the literature regarding accessibility and centralisation of cancer services in the light of the Calman-Hine report.	Systematic review and cross sectional study.	57 studies relating to accessibility and patient utilisation of services (not restricted to cancer services).	Distance and utilisation of: primary care, A&E, clinics & day cases, inpatients, visitors, and screening. Distance and: willingness to travel, mortality and morbidity.	3000 articles were identified and approximately 300 were screened against inclusion criteria of relevance, outcome and design. 243/300 papers were rejected. The quality of the evidence was generally poor with a lack of properly controlled trials. Direct evidence of the relationship between distance and mortality or morbidity was rare, although 2 studies of cancer patients indicated that outcomes are not affected by distance. 2 studies reported that patients are willing to travel some distance to overcome delays in accessing hospital services. The author concludes that "Overall the research evidence on the accessibility and centralisation trade-off is of relatively poor quality. There is some evidence both from the literature and from discussions with local purchasers that patients – once diagnosed as having cancer – will overcome sometimes considerable access difficulties."	Medline and 'other databases' searched, including those indexing unpublished studies. Researchers were also contacted for unpublished data. No language restriction. Studies relating to less developed countries or to mental health services were excluded. A wide range of studies are included across many countries, health care settings and patient groups.	2+
Finlayson et al. (1999)	To determine the strength of patient preferences for local care.	Cross sectional study.	100 patients (95% male, median age 65) awaiting elective surgery. Patients tended to be from rural locations. Patients with high anxiety or poor cognitive functioning were excluded. USA	Additional operative mortality risk that patients would accept to receive treatment locally.	Patients were presented with hypothetical clinical scenarios for surgical treatment of pancreatic cancer. Surgery could either be at the local hospital or at a regional centre (4 hours away by car), each option with known mortality risks. Risks were altered using a variation on the standard gamble technique. Patients preferred local surgery if the operative mortality risk at the local hospital were the same as the regional hospital (3%). If local operative mortality risk were 6% (twice the regional risk) 45 of 100 patients would still prefer local surgery. If local risk were 12%, 23 of 100 patients would prefer local surgery. If local risk were 18%, 18 of 100 patients would prefer local surgery.	The fact that 10% of patients would accept 100% mortality risk; suggests some patients either did not understand the concept of risk or did not answer the question truthfully.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					10% of patients said they would accept 100% local operative mortality rather than travel to the regional hospital for care. Authors' conclusions: Many patients prefer to undergo surgery locally even when travel to a regional centre would result in lower operative mortality risk. Therefore, policy makers should consider patient preferences when assessing the expected value of regionalizing major surgery.		

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Fitch *et al.* (2003)	To gather the views of patients on travelling for radiotherapy.	Cross sectional study.	64 breast cancer and 35 prostate cancer patients. 3 groups were included: those travelling long distances (400–1400km) for radiotherapy following re-referral from their local centre, those receiving radiotherapy within local travelling distances (0.5–120km), and those who lived in remote areas who had to travel long distances to their local centre. CANADA	Themes related to the travel experience were derived from patient interviews, using content and theme analysis.	Four travel related themes were reported: • Waiting was the most difficult part of the experience • The idea of travelling for treatment was distressing • Travelling for treatment was tiring and posed difficulties for patients. • Being away from home had both benefits and drawbacks. All patients reported a financial burden because of travel for radiotherapy. Authors' conclusions: Given the inevitability of travelling for radiotherapy, and the issues that arise for patients, supportive strategies need to be designed and implemented.	Canadian study: travel was over greater distances than those required in the UK Some supportive strategies to ease the burden of travel and staying away from home were proposed by patients.	3-
Guidry *et al.* (1997)	To estimate the effect of travelling distance to cancer treatment as a barrier to care.	Cross sectional study.	Patients diagnosed with breast, colon, cervical or prostate cancer or lymphoma within a network of 20 cancer treatment facilities. Cases were diagnosed between 1989 and 1993. Patients were at least 17 years of age. USA	Patients' perceptions of barriers to cancer treatment.	910 patients were identified as a systematic random sample drawn from more than 10000 patients with cancer. 593/910 (65%) surveys were returned. Perceived barriers to cancer treatment reported by patients: • distance from treatment 46% • access to car 48% • access to a driver 48% Patient groups with lower household income tended to report greater problems with transportation.		3+

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Kearney (2003)	To describe the experience of travelling to paediatric oncology centres.	Qualitative interviews and focus groups.	Four focus-group interviews of a total of 22 parents (17 mothers and 5 fathers) of children with cancer. UK & EIRE	Transcripts of focus group interviews.	The transcripts were analyzed qualitatively. Several burdens of travel were identified: Travelling with a sick child, worry of car accidents, financial problems (cost of second car, accommodation near the centre and time lost from work).	Author argues for devolution of care in sparsely populated areas.	4+
Meden *et al.* (2002)	To study the association between travel distance to radiotherapy and treatment for breast cancer.	Retrospective case series.	66 patients treated for breast cancer (stage I or II) from 1999–2000. Patients were identified from the medical records of 3 community hospitals. USA	Type of treatment (breast-conserving therapy (BCT) vs. modified radical mastectomy (MRM)).	Overall, BCT was utilised by 24% of patients. Patients who lived at greater distances from a radiation oncology unit were more likely to undergo MRM. Authors postulate that travel burdens include duration and expense of travel, and hazardous winter driving.	Association between travelling distance and the type of treatment could reflect differences between urban and rural populations (other than burden of travel).	3+
Teenage Cancer Trust: unpublished data (2004)		Cross sectional study.	Survey completed by 271 teenagers and young adults with cancer attending a conference. Age range 14–24 yrs. Information about diagnosis was available for 205 people. The group included 43 patients with 'bone-cancer', and 14 with STS. UK	Teenagers were questioned about their diagnosis, treatment history and their experience as a teenager with cancer.	Responses to the question “How long would you be prepared to travel for your treatment?” were: • Up to a couple of hours travel = 37% • Half a day’s travel = 8% • A day’s travel = 3% • Travel needing an overnight stay = 3% • Any distance and tim = 49%.		3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Wright *et al.* (1994)	To measure the strength of patient preference for high vs. low dose brachytherapy.	Case series.	90 female hospital staff and 38 patients with carcinoma of the cervix, at a regional cancer centre. 18 of the patients had been previously treated and 20 were newly diagnosed. CANADA	The association between patient characteristics (including travelling distance) and preference or high vs. low dose brachytherapy.	A questionnaire assessed preference for high vs. low dose brachytherapy (initially assuming that the two were equally effective). When both methods were assumed to be equally effective, only 34% of the 38 patients preferred three fractions of high dose rate to one fraction of low dose rate. However, when high dose rate was assumed to be 20% more curative, or 6% less toxic, a simple majority of 50% then said they would prefer high dose rate. Both preference and strength of preference for low dose rate were significantly associated with a greater travelling distance for treatments. Age, marital status, family structure, education, employment, and family income were not associated. Patients who lived further away from the treatment centre were most reluctant to choose three or more high dose rate fractions as compared with one or two low dose rate fractions. In the theoretical situation that high dose therapy was 4% more curative and 12% less toxic than the low dosage, the patients preferring the lower dosage & fewer visits tended to live further away from the treatment centre. Authors' conclusions: For our centre, for the comparison of three high dose rate fractions with one low dose rate fraction, and assuming both methods are equally effective, a majority of our patients would prefer to be treated with low dose brachytherapy. The high dose rate would have to be at least 2% more curative, or 6% less toxic, for at least 50% of the patients to prefer it over the low dose rate.	In a hypothetical treatment scenario travelling distance was related to a patient's choice of treatment.	3+

Table 1.b Psychosocial interventions

Abbreviations: STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Payne *et al.* (1997)	To provide psychological support and information to patients treated for STS. To gain information about quality of life issues in STS.	Intervention study.	12 patients treated for extremity STS with no recurrence. USA	Patients rated the value of the support group using a questionnaire.	No statistics presented. Patients reported decreased feelings of isolation, anger, depression and anxiety. The questionnaire indicated that patients felt the group interaction and relaxation elements the most helpful component of the sessions.		3-
May *et al.* (1979)	To describe an amputee visitor program for lower limb amputees.	Intervention study.	65 patients with cancer of the lower limb or limb girdle (51 with sarcoma) requiring amputation. 50% of patients were aged 20 or younger. USA	The long-term impact of the amputee visitor program on the patient and their family.	Patients were visited by a fellow amputee 5 days post-operatively, who was able to recount his or her own experience and answer questions. 60/65 (92%) of patients responded well to the visitor program. In follow up interviews with 36 of the patients, 33/36 (92%) said the visit substantially improved their outlook.	It is not clear how patients were selected for the program. It is not clear why only 36/65 patients were interviewed. The amputee visitor program appeared to be a useful adjunct to rehabilitation.	3-
Sarcoma UK: unpublished (data 2004)	To survey patients with sarcoma for their views on the support and information that they received during treatment.	Cross sectional study.	45 patients with sarcoma, 27 women and 18 men. UK	Medical care, patient information, emotional and practical support were given a quality rating of 0–10 by each respondent.	Counselling: 17/45 patients (38%) were offered counselling, and 6 took up the offer. 9 more patients sought counselling when it was not offered. 10 patients rated the value (out of 10) of the counselling they received; the average score was 8.7/10, with 4 patients rating it at 10/10. Support groups: 20/45 patients (44%) had no contact with other patients with sarcoma. 7/45 patients (15%) had attended a sarcoma specific support group, 14/45 patients (31%) had contact with other patients at hospital clinics. 76% found contact with other patients useful, although 9% reported such contact as negative.	Response rate is not reported.	3-

Table 1.c Information needs

Abbreviations: JAMA, journal of the American Medical Association; STS, soft tissue sarcoma; URL, uniform resource locator.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Biermann *et al.* (1999)	To evaluate the accuracy, ease, and variability of retrieving information on Ewing's sarcoma from a patient perspective	Observational study.	Four search engines available on Netscape™ to assess URLs given for the topic of Ewing sarcoma during a 4 week period.	Each Internet Web page evaluated for its relevance; presence or absence of medical information; whether information was anecdotal; whether information was peer-reviewed; source	371 unique URLs included. 170 pages contained medical information. 35% contained no reference to peer review. 58% contained information that was peer reviewed. Large variation in information e.g. survival rates reported ranged from 5% to 85%. Non-peer-reviewed articles were assessed for accuracy; 6% contained erroneous information. Also mildly misleading statements (not quantified) were found. Authors' conclusions: Although misleading or inaccurate information may be present on a small number of Web pages, the potential effects of such postings may have on vulnerable patients is of concern. In addition, inaccuracies may be contradictory to the information given by the physician, creating patient doubt and distrust.	Study conducted in 1999, world wide web content likely to have changed significantly. Frequency of agreement and inter-observer reliability between 2 observers evaluated. Crude appraisal of quality of sites. Not clear there was any attempt to validate claims for peer-review. Assessment for accuracy is not described. The first 25 websites listed by each of 7 search engines were evaluated.	3-
Fedora (1985)	To recount the experiences of a patient with osteosarcoma in a large teaching hospital.	Narrative account.	A female patient diagnosed with osteosarcoma of the lower extremity at the age of 16. The patient initially had limb salvage surgery and then amputation following infection. The account was published 9 years later, when the patient was working as a cancer nurse. USA		"Fear of the unknown was perhaps my greatest source of anxiety throughout the duration of hospitalizations." "My level of anxiety was reduced and my sense of security was increased by knowing what to expect before tests and procedures. I wanted no surprises." "Nurses can help eliminate unnecessary fears by offering detailed explanations of planned tests and procedures, and explanations of any changes in patients' expectations of care. If the		4

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					nurse is unaware or uncertain of the correct information, efforts to obtain it are appreciated as actions showing true concern."		
Kaiser (1988)	To discuss the treatment and rehabilitation needs of patients with bone sarcoma.	Review.			Information needs identified by the author: Most patients want detailed information about procedures, test results, treatment plans and expected outcomes. Supplying this information increases patients' security and sense of control, as does including them in decision making. Medical staff should take cues from patients in order to supply them with the type and amount of information they require, without overwhelming them.		4
Payne *et al.* (1997)	To describe a pilot support group intervention based upon a thematic counselling model for patients treated for STS; intervention evaluated by participants.	Observational study.	2 groups of STS patients; comprising 8 patients and 4 patients respectively. Intervention focused on issues which patients had identified as areas of concern. Emphasis on giving medical information, improving coping and problem solving skills and teaching relaxation and stress management. USA	Description of project; participant-reported rating of the value of each aspect of the programme.	Common themes reported by patients were: communication with family, friends and physicians, anxiety about lack of information about STS, and major financial disruption because of their illness. At the conclusion patients reported that feelings of isolation, anger, depression, and anxiety significantly decreased; and their level of self-confidence increased dramatically. Authors' conclusions: The pilot support group intervention is recommended as a model for enhancing the quality of life of patients with STS.	Very small sample size. Conclusions are not based on statistical analysis of data.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Rao (2003)	To assess patients' needs for web based information on STS. To examine the quality of STS information on the internet.	Observational study.	13 patients attending the sarcoma follow up clinic of a single institution. UK	Patients' need for information, willingness and ability to use the internet to obtain this information. The quality and popularity of 23 STS websites, using JAMA benchmarks.	Patients' information needs: • 5/13 (38%) of patients would have liked more information on an aspect of STS. • 6/13 (46%) said they would visit an STS website if it was recommended. • 6/13 (46%) had access to the internet at home. Website quality (23 websites appraised): • Display of authorship of medical content: 7 websites (30%). • References: 7 (30%) • Date of update: 13 (57%) • Disclosure of page ownership or sponsorship: 16 (70%) • Health on the Net seal: 5 (22%) • Disclaimer: 12 (52%) Author's conclusions: Patients with STS seem inclined to use the internet for more information. The general quality of information about STS on the internet is poor but there are some good sites, namely those from the main cancer organisations.	Small sample size. Relatively small number of websites appraised.	3-
Sarcoma UK: unpublished data (2004)	To survey patients with sarcoma for their views on the support and information that they received during treatment.	Observational study.	45 patients with sarcoma, 27 women and 18 men. UK	Medical care, patient information, emotional and practical support were given a quality rating of 0–10 by each respondent. Patients were also asked about the provision of information during their treatment.	69% of the 45 respondents said that they sought information about their disease on the internet. 27% of the respondents had sought information from the cancer charity Cancer BACUP. 18% of the patients said they had been offered general information about sarcoma during their treatment, although patients rated highly the information given by doctors about their own situation.	Response rate is not reported.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Teenage Cancer Trust: unpublished data (2004)	To survey the views of teenagers with cancer on their treatment.	Observational study.	Survey completed by 271 teenagers and young adults with cancer attending a conference. Age range 14–24 yrs. Information about diagnosis was available for 205 people. The group included 43 patients with 'bone-cancer', and 14 with STS. UK	Suitability of information for teenagers.	Responses to the question "was the information given to you about your cancer suitable for someone of your age?" were: • Aimed at people older than me 27% • Aimed at people my age 54% • Aimed at people younger than me 19% 66% of those surveyed were not provided with fertility counselling. Of those who received fertility counselling 52% were satisfied with it. Response to the question "Who told you that you had cancer?": • GP 6% • Hospital doctor 70% • Nurse 3% • Parent 21% Responses to the question "What choices, if any, were for treatment options?": • All choices given 19% • Some choices given 25% • No choices given 56%	Unpublished.	3-

Diagnosis

The questions

a) For people with lumps suspicious of sarcoma, does referral to a specialist sarcoma unit or MDT improve the rate of pre-operative diagnosis?

b) In people with suspected osteosarcoma, does an urgent referral for an X-ray result in an earlier accurate diagnosis?

c) Does diagnosis of sarcoma by a specialist radiologist, compared with a general radiologist, lead to greater diagnostic accuracy?

d) In people with STS, does early referral improve survival?

e) Do delays in diagnosis result in poor outcomes for people with sarcoma?

f) Are current guidelines for early diagnosis of STS resulting in improved outcomes for patients?

Nature of the evidence

a) Specialist pre-operative diagnosis

Seven observational studies compared the preoperative management of people with sarcoma in specialist and non specialist settings. Four of the studies described institutional case series; two were audits of cancer registry data, and one was a survey of surgeons. Two of the studies included people with lumps suspicious of sarcoma; the remainder included only those with confirmed bone or soft tissue sarcoma.

Specialist centres were variously defined as: containing a multi-disciplinary team devoted to managing sarcomas (Bauer *et al.* 2001; Rydholm *et al.* 1983), a treatment centre with an orthopaedic oncologist member of the Musculoskeletal Tumour Society (Mankin *et al.* 1996), the musculoskeletal tumour service of an orthopaedic surgery department (Pollock & Stalley 2004), a regional referral centre for people with sarcoma (Grimer & Sneath 1990; Nijhuis *et al.* 2001), or a unit with a surgeon with a special interest in sarcomas (Serpell & Pitcher 1998;

Glencross *et al.* 2000). Centres which did not meet these criteria were considered non-specialist.

b) In patients with suspected osteosarcoma, does an urgent referral for an X-ray result in an earlier accurate diagnosis?

A Swedish case series of good quality directly examined the associated between initial ordering of a radiograph and diagnostic delay in osteosarcoma and Ewing's sarcoma (Widhe & Widhe 2000). A poor quality US case series of pelvic bone sarcomas included information about diagnostic delay and initial referral for a radiograph, but did not examine the association between them (Wurtz *et al.* 1999). Three UK case series of good quality and a US one of poor quality considered pre-referral imaging as a source of diagnostic delay in soft tissue and bone sarcomas (Aboulafia *et al.* 2002; Ashwood *et al.* 2003; Goyal *et al.* 2004; Barlow & Newman 1994).

c) Does diagnosis of sarcomas by a specialist radiologist, compared with a general radiologist, lead to greater diagnostic accuracy?

Three UK case series of good quality and a US case series of poor quality reported audits by sarcoma treatment centres of the adequacy of pre-referral imaging (Aboulafia *et al.* 2002; Ashwood *et al.* 2003; Saifuddin *et al.* 2000; Grimer & Sneath 1990). A UK study compared the frequency of preoperative imaging in cancer centres with that in district general hospitals and cancer units for people with sarcoma (Glencross *et al.* 2000). One UK study of good quality reported a comparison of the original radiological reports with reviews by a specialist oncological radiologist (Loughrey *et al.* 1999) but only 6% of patients in this study had sarcoma.

d) In people with STS, does early referral improve survival?

No studies addressed the question directly, although a case series from the Scandinavian Sarcoma Group (Bauer *et al.* 2004; Bauer 2004) included a historical comparison of referral practices and patient outcomes. Other evidence was included to help estimate referral delay in STS. A UK study (Lothian *et al.* 2003) used regional cancer registry data to describe delays in the secondary and tertiary referral of people with sarcoma. Two case series of good quality (Ashwood *et al.* 2003; Clark & Thomas 2005) reported delay in referral (but not

survival) for people with STS. Two poor quality studies reported the number of GP visits before secondary referral (Aboulafia *et al.* 2002; Teenage Cancer Trust: unpublished data 2004).

e) Do delays in diagnosis result in poor outcomes for people with sarcoma?

No population based studies of diagnostic delay and outcome in people with sarcoma were identified. Nine observational studies (case series) analysed diagnostic delay in terms of disease stage at diagnosis (Ashwood *et al.* 2003; Bacci *et al.* 1999; Bacci *et al.* 2000; Brouns *et al.* 2003; Simpson *et al.* 2005) or survival (Clasby *et al.* 1997; Goyal *et al.* 2004; Wurtz *et al.* 1999; Sneppen & Hansen 1984; Durve *et al.* 2004) in people with sarcoma.

Two case series evaluated tumour size as a prognostic factor (Pisters *et al.* 1996; Ramanathan *et al.* 1999) plausibly, if indirectly, related to diagnostic delay. Three studies reported outcomes in people with misdiagnosed sarcoma (Grimer & Sneath 1990; Muscolo *et al.* 2003; van Dalen 2000).

If diagnostic delay is defined as the interval between the onset of symptoms and correct diagnosis, it consists of both patient-related and doctor-related components. Fourteen case series and one cross sectional study attempted to quantify the patient-related and doctor-related components of diagnostic delay in people with sarcoma (Ashwood *et al.* 2003; Bacci *et al.* 1999; Bacci *et al.* 2000; Bergh *et al.* 2001; Brouns *et al.* 2003; Clasby *et al.* 1997; Goyal *et al.* 2004; Grimer & Sneath 1990; Lawrence, Jr. *et al.* 1987; Lothian *et al.* 2003; Sneppen & Hansen 1984; van Dalen 2000; Widhe & Widhe 2000; Wurtz *et al.* 1999; Simpson *et al.* 2005).

f) Are current guidelines for early diagnosis of STS resulting in improved outcomes for patients?

Two case series of good to poor quality (Bauer *et al.* 2004; Bauer 2004), described the introduction of the Scandinavian Sarcoma Group (SSG) referral guidelines and the associated changes in referral practices and patient outcomes. A paper describing the development and dissemination of the SSG guidelines (Rydholm 1997) was also included.

One systematic review (Lewis *et al.* 2005) examined audits of the compliance of GPs with referral guidelines for suspected sarcoma. Two case series addressed compliance with diagnostic guidelines in Dutch (Nijhuis *et al.* 2001) and French (Ray-Coquard *et al.* 2004) regions. An audit of a UK STS treatment unit (Hussein & Smith 2005) reported the proportion of patients with symptoms consistent with those in the NICE referral guidelines for suspected sarcoma.

Summary of the supporting evidence for the recommendations

a) Pre-operative diagnosis in specialist and non-specialist settings

The evidence suggests that an accurate and safe pre-operative diagnosis of sarcoma is more likely at a specialist centre. The diagnostic clinic for STS closely affiliated to (but geographically separate from) the specialist sarcoma MDT is a new service model and no direct evidence was identified.

Preoperative biopsy

The UK audit study of Glencross and co-workers (Glencross *et al.* 2000) observed that 96% of people referred to a surgeon with special interest in sarcoma were biopsied before surgery compared to 56% of those referred elsewhere. In the US study of Mankin and co-workers (Mankin *et al.* 1996), biopsy was adequate in 96.5% of cases in specialist centres compared to 86.1% of cases in other centres. Pollock and Stalley (Pollock & Stalley 2004) reported that 97% of specialist biopsies were adequate compared to 72% of those done at referring institutions. However, a large UK case series (Hoeber *et al.* 2001), observed equivalent quality of core-needle (Tru-cut) biopsy cores from limb or limb girdle sarcomas obtained in referring hospitals and in a specialist STS unit, and its authors suggested that the successful performance of Tru-cut biopsy may not be dependent on the volume of the doctor's experience. In the Netherlands the study by Nihuis and co-workers (Nijhuis *et al.* 2001) reported that in a specialist centre 64% of people were biopsied in accordance with guidelines compared with only 29% people investigated in other centres.

A number of studies reported biopsy complication rates. Mankin and co-workers (Mankin *et al.* 1996) noted that 4.1% of specialist biopsies resulted in an adverse alteration in the treatment plan compared to 36.3% of non-specialist biopsies. The

study also noted that 3.5% of specialist biopsies had an unfavourable influence on the patient's outcome compared to 17.4% of non-specialist biopsies. Grimer and Sneath (Grimer & Sneath 1990) reported that approximately 5% of biopsies performed in the specialist centre were unsatisfactory (resulting in complications or alteration of the treatment plan) compared with 60% of biopsies of malignant bone tumours carried out in non specialist referring hospitals. A suboptimal site hindered definitive treatment following 2% of specialist biopsies compared to 38% of non-specialist biopsies in the Pollock and Stalley study (Pollock & Stalley 2004). In the series reported by Serpell and Pitcher (Serpell & Pitcher 1998) there were no complications following specialist biopsies compared to complications after 63% of non-specialist biopsies.

None of the included studies adjusted for the confounding effect of case mix differences between specialist and non-specialist treatment centres. For example, people with small superficial tumours are less likely to have a sarcoma, and may justifiably be more likely to be treated with excisional biopsy at a non specialist centre. Studies published by specialist centres sometimes use patients referred after treatment elsewhere as a comparison group to those managed exclusively at the specialist unit. People with disease that is difficult to treat, however, may be more likely to be referred to the specialist treatment centres and may not be representative of patients treated at non specialist hospitals.

Preoperative Imaging

The UK audit study of Glencross and co-workers (Glencross *et al.* 2000) observed that 92% of people with sarcoma referred to a specialist centre had CT or MR imaging before surgery compared to 56% of those referred elsewhere. Case mix could account for some of this discrepancy since people with small superficial tumours may be less likely to have complex imaging or be referred to a specialist centre.

Accuracy of preoperative diagnosis

In Mankin and co-workers' study (Mankin *et al.* 1996) diagnosis was accurate in 86.7% of cases in specialist centres compared to 72.6% of cases in non-specialist centres. Rydholm and co-workers (Rydholm *et al.* 1983) reported that

the tentative preoperative diagnosis was falsely negative (benign) in 11% of people with sarcoma treated in a specialist centre compared to 67% of those treated elsewhere. Evidence on the diagnostic accuracy of specialist and non-specialist pathologists is discussed in the pathology section.

b) In people with suspected osteosarcoma, does an urgent referral for an X-ray result in an earlier accurate diagnosis?

Limited, but consistent, evidence supports the early ordering of a radiograph in people with suspected osteosarcoma. In the Swedish study of Widhe and Widhe (Widhe & Widhe 2000) the ordering of a radiograph by the referring physician was associated with a shorter delay in diagnosis in a case series of 102 people with osteosarcoma and 47 with Ewing's sarcoma. In a UK case series of 68 people with osteosarcoma and 35 with Ewing's sarcoma (Goyal *et al.* 2004), presentation of the patient to Accident & Emergency more commonly led to immediate X-rays than with a GP consultation. Diagnosis was less delayed in those presenting to A&E than in those presenting to a GP, although there are likely to be important differences in the case mix of these two groups. In a US case series of 68 primary pelvic bone sarcomas, which included 16 osteosarcomas, the sarcoma was discovered as an abnormality on an initial radiograph of 49/68 patients before any other imaging was made (Wurtz *et al.* 1999). An audit of the Leeds Bone Tumour Registry (Barlow & Newman 1994) estimated that initial failure to order a radiograph was responsible for diagnostic delay in 4% of people with primary bone tumours of the shoulder.

Complex imaging studies (CT, MRI or bone scan) ordered by referring physicians for putative bone sarcomas were often inappropriate (Aboulafia *et al.* 2002) or inadequate (Ashwood *et al.* 2003), and were a potential source of referral delay.

c) Does diagnosis of sarcomas by a specialist radiologist, compared with a general radiologist, lead to greater diagnostic accuracy?

There was some evidence to suggest shortcomings in radiological assessment of people with sarcoma in referring hospitals, but no direct comparisons with specialist radiologists were reported. A UK observational study (Grimer & Sneath 1990) found that 19% of bone tumours referred to a specialist bone tumour treatment service had been missed by both the clinician and radiologist on the

initial radiograph, although the tumour was evident on retrospective review of the image. Outcomes were poorer in the group of patients whose initial radiographs were erroneously reported as normal; diagnostic delay meant that 58% required amputation or were inoperable compared to 15% of those whose initial radiographs were interpreted correctly.

Three observational studies (Aboulafia *et al.* 2002; Ashwood *et al.* 2003; Saifuddin *et al.* 2000) found the technical adequacy of CT or MRI imaging performed at referral centres was often poor. A tendency towards excessive imaging was also observed. Two studies (Loughrey *et al.* 1999; Saifuddin *et al.* 2000) noted that reporting of MRI and CT studies performed at referral centres was often incomplete, failing to include tumour dimensions and information about lung, liver and bone involvement. An audit of the management of sarcoma in one English health region (Glencross *et al.* 2000) noted that preoperative cross-sectional imaging was more often omitted in district general hospitals (DGHs) or cancer units than in specialist cancer centres.

d) In people with STS, does early referral improve survival?

No direct evidence relating referral delay to patient outcomes was identified. A study of patients at a Scandinavian STS treatment centre (Bauer 2004; Bauer *et al.* 2004) reported patient outcomes over a period of 15 years. Improvements in referral practices were accompanied by better five year local control and survival rates. The analysis was not case mix adjusted and the improvements in outcomes seen at the specialist centre could be due to increased referral of patients with good prognosis.

There is observational evidence which suggests that diagnostic uncertainty at the point of consultation to primary or secondary care can result in a delay in referral to the appropriate treatment centre. In a study of referral to a UK specialist STS unit (Clark & Thomas 2005), delay of more than three months was seen in 20% of patients. Median delay in this subgroup was 14 months. The most frequently identified reason for delay was lack of clinical suspicion at the initial consultation. A second UK study (Ashwood *et al.* 2003) reported referral delay of people with malignant bone or soft tissue tumours to a specialist treatment centre. On

average, referral to the treatment centre from the person's GP or local hospital took 7.5 months.

A study (Lothian *et al.* 2003), using data from the Northern & Yorkshire Cancer Registry, examined referral patterns for 362 people with non-gynaecological sarcoma in the years 1999–2000. Only 60% of these people were eventually referred to a specialist sarcoma treatment centre, many experiencing considerable delay in the process. Mean delay was 52 days in secondary referral (range was 0–678 days) and 77 days in tertiary referral (range was 0–414 days).

There is limited observational evidence that on average approximately five visits are made to a GP before a patient with sarcoma is referred elsewhere (Aboulafia *et al.* 2002; Teenage Cancer Trust: unpublished data 2004).

e) Do delays in diagnosis result in poor outcomes for people with sarcoma?

Evidence relating diagnostic delay to patient outcomes in sarcoma was limited in quantity and observational in nature. The studies tended to include small numbers of heterogeneous patients, making it difficult to estimate the prognostic significance of delay.

UK studies reporting the early management of people with sarcoma (Ashwood *et al.* 2003; Clark & Thomas 2005; Grimer & Sneath 1990) express the opinion that diagnostic delay has a detrimental effect on treatment options and outcomes. Indirect support is provided by large case series of American and British people (Pisters *et al.* 1996; Ramanathan *et al.* 1999) with STS which identify larger tumour size as an independent adverse prognostic factor.

In a UK study of people with STS (Clasby *et al.* 1997), which partially adjusted for case mix, preoperative duration of symptoms for more than a year was associated with better survival. This suggests diagnostic delays may be a feature of lower grade tumours. This notion is supported by four other studies of people with bone and soft tissue tumours which found patient and referral delays tended to be longest for people with benign tumours and shortest for those presenting with metastatic disease (Ashwood *et al.* 2003; Bacci *et al.* 1999; Bacci *et al.* 2000; Brouns *et al.* 2003). The audit of Hussein and Smith (Hussein & Smith 2005)

noted delays were longest for people with slow growing tumours. A further four studies did not observe a significant relationship between diagnostic delay and survival in people with sarcoma (Durve *et al.* 2004; Goyal *et al.* 2004; Sneppen & Hansen 1984; Wurtz *et al.* 1999), although Simpson and co-workers (Simpson *et al.* 2005) reported an association (at p=0.10) between diagnostic delay and more advanced disease stage in people with Ewing's sarcoma of the upper extremity.

There is observational evidence that delays and inappropriate treatment following misdiagnosis can have an adverse effect on the outcome of people with sarcoma. Three studies (Grimer & Sneath 1990; Muscolo *et al.* 2003; van Dalen 2000) reported adverse outcomes in people who had been misdiagnosed and managed inappropriately. A UK study (Grimer & Sneath 1990) reported that, as a consequence of diagnostic delay, people with malignant bone tumours that were missed on the on their initial radiograph were more likely to require amputation or be deemed inoperable, than those whose initial radiographs were interpreted correctly. In an Argentinean series of people with misdiagnosed musculoskeletal tumours (Muscolo *et al.* 2003), 60% of patients required a more radical surgical procedure than would originally have been necessary due to diagnostic delay or contamination of the tumour margins. A Dutch population-based study (van Dalen 2000) of retroperitoneal STS reported that complete resection of the tumour was less likely in people with a preoperative misdiagnosis than in those in which the diagnosis of sarcoma was considered. This was partly because unnecessary surgery for an inoperable tumour was more likely in those with preoperative misdiagnosis.

Duration of patient-related delay in diagnosis

In a Belgian study (Brouns *et al.* 2003) 47% of people with STS showed delay of more than one month before seeking medical advice. The median delay in this subgroup was 4 months. In a Dutch study (van Dalen 2000) 36% of people with retroperitoneal STS waited for more than 6 months following the onset of symptoms before seeing a doctor. The average patient delay in a small UK study (Ashwood *et al.* 2003) of people with malignant bone or soft tissue tumours was 7.6 months.

The shortest patient delays were reported for people with osteosarcoma; estimates ranged from 1 to 1.6 months (Bacci *et al.* 2000; Goyal *et al.* 2004; Grimer & Sneath 1990; Sneppen & Hansen 1984; Widhe & Widhe 2000). Estimates of patient delay were longer for those with Ewing's sarcoma, ranging from 1.5 to 6 months (Bacci *et al.* 1999; Goyal *et al.* 2004; Grimer & Sneath 1990; Sneppen & Hansen 1984; Widhe & Widhe 2000; Simpson *et al.* 2005).

Duration of doctor-related delay in diagnosis

Estimates of doctor-related diagnostic delay were shortest for osteosarcoma, ranging from 1.2 to 2.25 months (Bacci *et al.* 2000; Goyal *et al.* 2004; Grimer & Sneath 1990; Widhe & Widhe 2000). Longer doctor related diagnostic delays were reported for people with Ewing's sarcoma of bone (1.25 to 7.75 months) (Bacci *et al.* 1999; Goyal *et al.* 2004; Grimer & Sneath 1990; Widhe & Widhe 2000; Simpson *et al.* 2005). One US study found that 44% of people with primary pelvic bone sarcomas experienced a doctor-related diagnostic delay greater than a month (Wurtz *et al.* 1999). Median delay was seven months in this group.

An US study reported that 50% of people with STS experienced a doctor related diagnostic delay of two months or more (Lawrence, Jr. *et al.* 1987). In 21% of patients delay was more than six months. Similarly in a Belgian study, doctor related delay of more than one month was seen in 27% of people with STS (Brouns *et al.* 2003). The median delay in this subgroup of patients was 6 months.

f) Are current guidelines for early diagnosis of STS resulting in improved outcomes for patients?

There is limited evidence, from the Scandinavian Sarcoma Group, to suggest that the introduction of referral guidelines may improve outcomes. Following the introduction of the Scandinavian Sarcoma Group referral guidelines for STS the rate of primary referral before surgery or biopsy improved from 69% in the period 1986–1989 to 84% in the period 1999–2001 in Norway and Sweden (Bauer *et al.* 2004). Better referral practices were accompanied by improved 5 year local control and survival rates at specialist centres (Bauer 2004). The analysis was not case mix adjusted, however, so the improvements in outcomes seen at the specialist centres could be due increased referral of patients with good prognosis.

In two other European studies the introduction of guidelines for the early management of people with sarcoma met with limited success. A study in the North-Netherlands region (Nijhuis *et al.* 2001) measured compliance with diagnostic guidelines for STS stating that incisional biopsy should be performed for tumours larger than 3 cm. Adherence to these guidelines was poor; 63% compliance in a tumour treatment centre and 29% compliance in district hospitals. In a study conducted in one French region (Ray-Coquard *et al.* 2004) compliance with FNCLCC diagnostic guidelines at initial biopsy was 65% and at initial surgery 52%. Diagnostic biopsy was performed in only 42% of people with STS and only 44% of patients had adequate initial wide surgical margins.

The success of the Scandinavian guideline in comparison to those of the French and Dutch may be due in part to its dissemination. Information was given to medical students during the course of their pathology, orthopaedic and general surgical training; lectures were given repeatedly at referring hospitals and feedback was given to referring clinicians (Rydholm 1997). The authors of both the French and Dutch studies commented that guideline dissemination was poor in their regions (Nijhuis *et al.* 2001; Ray-Coquard *et al.* 2004).

The audit of Hussein and Smith (Hussein & Smith 2005) revealed that 95% of patients had at least one of the symptoms listed in the NICE referral guidelines for suspected STS. Despite this the average delay between onset of symptoms and specialist treatment was 21 months. The authors speculated that referral pathways for people with suspected STS needed to be simplified.

A systematic review (Lewis *et al.* 2005) of audits of GP referrals for suspected cancer reported 6 studies which included some people with sarcoma. Four were conducted by general hospitals, two by primary care trusts and one by a teaching hospital and all were conducted between 2001 and 2003. The conformity of GP referral to the symptoms listed in the referral guidelines ranged from 60% to 100% for putative sarcoma. Diagnostic delay and patient outcomes were not reported.

Table 2.a Pre-operative diagnosis at specialist and non-specialist centres

Abbreviations: MDT, multidisciplinary team; NSCAG, National Specialist Commissioning Advisory Group; RR, relative risk; STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Mankin *et al.* (1996)	To determine the frequency of errors, complications, alterations in outcome of biopsies of primary malignant musculoskeletal sarcomas FOLLOW UP TO PREVIOUS SIMILAR STUDY, (1982).	Retrospective case series.	25 surgeons from 21 institutions submitted cases of 597 patients. 235 cases (39%) were STS and 362 (61%) bone sarcomas USA.	Errors in diagnosis, non-representative biopsies, complications of the biopsy, alterations in treatment and outcomes, accuracy of needle biopsy.	Comparisons of biopsy outcomes (musculoskeletal treatment centres vs. referring institutions): • Error in diagnosis: 39/316 vs. 77/282 (13.3% vs. 27.4%, RR:0.45) • Inadequate biopsy: 11/316 vs. 39/282 (3.5% vs. 13.9%, RR:0.25) • Alteration of treatment plan: 13/316 vs. 102/282 (4.1% vs. 36.3%, RR:0.11) • Change in the course or outcome: 11/316 vs.49/282 (3.5% vs. 17.4%, RR:0.20) Authors' conclusions: Authors make recommendations about ensuring adequacy of representative tissue on biopsy; interpretation by a suitably experienced pathologist; referral to a treatment centre if local arrangements are not adequate.	Treatment centre biopsies were defined as those performed by orthopaedic oncologist members of the Musculoskeletal Tumour Society. Unclear what proportion of surgeons responded to the questionnaire.	3+
Nijhuis *et al.* (2001)	To analyse of how well national diagnostic guidelines for STS are being used in one region of Holland	Retrospective observational study – clinical audit.	351 STS patients 1989-96. Exclusions: gastro-intestinal STS, urogenital STS, Kaposi sarcoma. Patients were identified from a population based registry. NETHERLANDS	Adherence to diagnostic and referral guidelines. Adequacy of biopsy vs. case volume.	Adherence to guidelines significantly better in specialist centre. In district hospitals, patient volume had no significant influence on compliance with guidelines, except for management of patients with STS >3cm. Comparison of conformity to biopsy guidelines: (specialist treatment centre vs. all other centres) 32/50 vs. 53/183 (64% vs. 29%).	Specialized sarcoma centre is defined as the regional referral centre for patients with sarcoma.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					In district hospitals, where fewer than 15 patients were treated in 7 years, an inadequate biopsy procedure or even no biopsy was performed significantly more often prior to resection. Older patients (>60 years) were significantly less likely to be referred to a specialist centre. Authors' conclusions: In many aspects of the diagnostic process of STS, existing guidelines were not followed, especially in community hospitals. Adherence to all individual guidelines was significantly better in the specialized centre. Concentration of patients with STS in a limited number of hospitals and intensified collaboration with specialised centres seem advisable.		
Rydholm *et al.* (1983)	To analyse the methods used in the diagnosis and treatment of STS, and variations of these methods over time and setting.	Retrospective case series.	261 patients with STS in trunk and extremities 1964–1981. Centre opened in 1970. Patients treated by specialist centre were separated into patients referred before and after surgery. SWEDEN	Resection margin and diagnostic accuracy.	In the period 1971–1980, 111/142 patients treated by the Centre eventually had R0 (wide or compartmental) resection compared to 15/46 of the patients treated outside Centre (78% vs. 32%, RR: 2.44). Amputations (centre vs. other institutions) : 15/142 vs. 13/46 (11% vs. 28%). When recorded, the tentative pre-operative diagnosis was falsely negative (benign) in 8/70 patients treated by the Centre compared to 67/107 of the patients treated outside the Centre (11% vs. 67%, RR: 0.16). Over the years 1964–1981 the number of patients referred increased. Authors' conclusions: Patients should be seen by a specialized group for 2 reasons. Firstly because clinical findings	Some data in this study are 40 years old. Specialized sarcoma group (MDT?) defined as consisting of representatives from orthopaedic surgery, clinical pathology, clinical cytology, diagnostic radiology and oncology. Where there was uncertainty over surgical margins, the lower class was chosen. Statistical analysis is not used.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					and imaging are more easy to interpret for an untouched tumour. Secondly marginal excision or incisional biopsy performed improperly may compromise the definitive surgery and lead to poorer outcomes.		
Grimer & Sneath (1990)	To highlight problems in the early management and diagnosis of malignant bone tumours.	Case series.	70 patients with malignant bone tumours referred to a single bone tumour treatment centre during 1 year. UK	Patient delay, diagnostic delay, sensitivity of initial X-ray diagnosis, biopsy errors.	Authors report that about half the biopsies were carried out before referral to the centre. Of these only 40% were entirely satisfactory. In many cases the biopsy had been carried out by a junior surgeon and with little regard to the definitive surgical procedure. Complications from the non specialist biopsy included infection of the track, transgression of an adjacent joint, inconvenient site for subsequent surgery and, in several cases, dissemination of the tumour into previously uninvolved tissue compartments. In 2 cases insufficient material was obtained from the biopsy and in 6 cases an inexperienced pathologist misinterpreted the histology. Authors' conclusions: Problems were almost ten times as common when biopsies are carried out in the referring centre. Any patient suspected of having a bone tumour should be immediately referred to a bone tumour treatment service before biopsy. This should ensure speedy and appropriate treatment, with staging and biopsy carried out by the surgical team responsible for the definitive procedure.	Specialist centre was NSCAG designated bone tumour treatment service.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Hoeber *et al.* (2001)	To compare the accuracy of incision biopsy with Tru-cut biopsy for limb and limb girdle STS.	Retrospective case series.	570 patients (576 lesions), referred to Royal Marsden Hospital NHS Trust (RMH) from 1989 to 1998. Series included 8 STS chondrosarcoma and 1 bony chondrosarcoma. UK	Diagnostic accuracy of Tru-cut and incision biopsy.	Overall Tru-cut biopsy differentiated benign from malignant tumours with a sensitivity of 99.4%, specificity 98.7%, positive predictive value 99.4%, and negative predictive value 98.7% with similar results for RMH and referral hospitals. Tru-cut identified both tumour subtype and grade in approximately 80% of STS. Incision biopsy had similar sensitivity and specificity for differentiating benign from malignant soft tissue tumours as well as subtype of STS but was less accurate for grade assessment. Authors conclusions: Tru-cut biopsy is equally as effective as incision biopsy and has a lesser morbidity. Smaller STS are at greatest risk of enucleation (excision biopsy) and inappropriate management. The quality of the Tru-cut cores obtained was equal at the RMH to the referring hospitals, suggesting the technique may not be dependent on case volume or expertise.	Histology of the resected specimens was the reference standard diagnosis.	3+
Pollock & Stalley (2004).	To examine the early management of patients biopsied for musculoskeletal tumours.	Prospective case series.	All patients (n=144) referred to the musculoskeletal tumour service of an Orthopaedic Surgery Department during 2002. 48 malignant and 35 benign bone tumours; 29 malignant and 30 benign soft tissue tumours. AUSTRALIA	Alterations in treatment and patient outcomes following biopsy either in a referring institution or a recognized treatment centre.	Comparisons between outcomes at musculoskeletal tumour service and referring institutions: • Suboptimal biopsy site significantly hindering definitive treatment: 2/113 vs. 11/29 (2% vs. 38%, RR: 0.05, p<0.01). • Adequate material at biopsy: 110/113 vs. 21/29 (97% vs. 72%, RR: 1.34, p<0.01). • Amputation rate (for malignant lesions): 3/57 vs. 4/20 (7% vs. 25%, RR: 0.28, p<0.03).	The authors acknowledge the selection bias - the patients referred could be difficult diagnostic cases, but no case mix adjustment is made.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: There is a high complication rate when patients with musculoskeletal tumours are biopsied by surgeons inexperienced in their management. These patients are better served by early referral to a specialist centre where staging investigations can be performed with minimal morbidity.		
Serpell & Pitcher (1998)	To analyze the referral patterns of patients with STS, the accuracy of core biopsy, complications associated with biopsy and the eventual surgery required.	Retrospective case series	45 patients with suspected sarcoma referred to 2 surgeons with a special interest in STS between 1991 and 1996. Eventual diagnosis was STS for 24 patients, benign soft tissue tumour for 20 patients and secondary carcinoma in one patient. AUSTRALIA	Accuracy of core biopsy, complications of biopsy.	37/45 (82%) of patients were referred with their tumour intact, of these 31 (84%) underwent core biopsy. The overall accuracy of core biopsy was 84%. The sensitivity was 94%, with 100% specificity. 8/45 (18%) patients were biopsied prior to referral (6 incisional and 2 excisional). Complications due to the biopsy led to management problems in 5/8 (63%) of the patients biopsied prior to referral. No complications were reported in the 31 patients who received core biopsy after referral. Authors' conclusions: Core biopsy is the diagnostic procedure of choice for suspected STS.	Low number of sarcomas seen by each surgeon (average of 2 per surgeon per year). Gold standard was histological examination of the resected tumour. 3 patients did not have definitive surgery.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Glencross *et al.* (2000).	To conduct a baseline audit of the patterns of care for patients with sarcoma in the Trent region.	Case series.	204 patients with STS registered in the Trent region 1995–1997. UK	Preoperative investigations received by patients referred to a sarcoma "expert" compared to those received by patients referred elsewhere.	For patients having surgery, proportion of preoperative investigations for those referred to sarcoma specialist vs. those referred elsewhere: • CT or MRI: 23/25 (92%) vs. 51/135 (37%) • Biopsy taken: 24/25 (96%) vs. 98/179 (56%) • Record of tumour size in notes: 18/25 (72%) vs. 142/179 (79%) Author's conclusions: All clinicians should follow management guidelines and proposals to set up referral centres should be considered.	Abstract only, audit reported more completely in Glencross et al. (2003) but without the specialist vs. non-specialist analysis. The sarcoma specialist was a surgeon with a special interest in sarcoma.	3-

Table 2.b Urgent referral for an X-ray in people with suspected osteosarcoma.

Abbreviations: A&E, Accident and Emergency; CT, computerized tomography; MRI, magnetic resonance imaging; SI, symptom interval; STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Ashwood *et al.* (2003)	To investigate the sources of delay in diagnosis and determine if there was a similar diagnostic error rate as found by the Musculoskeletal Tumour Society, which subsequently altered patients' management and affected outcome.	Prospective case series.	100 consecutive patients referred to a supra-regional bone and STS service. UK	Delay in referral to the bone tumour unit. Radiograph prior to referral. Inappropriate or inadequate imaging. Biopsy complications.	100 patients overall with 41 benign, 47 sarcoma and 9 metastatic tumours. Average referral delay for each tumour category: • All tumours 13.5 months (range 0–32 months) • Malignant 7.5 months (range 0–13 months) • Metastatic <5 months • Benign >20 months Imaging prior to referral: Plain radiograph: 96/100 (96%). Complex imaging (MRI or CT) 63/100 (63%). 56/63 (89%) of complex imaging studies were inadequate and had to be repeated (contributing to the referral delay). In 7/47 (15%) of cases seeding of tumour was risked by poorly positioned needle (5) and open biopsies (2) that contaminated intra-articular components. Authors' conclusions: Delay in diagnosis may allow the tumour size to increase – a factor associated with poor outcome. Following a plain radiograph, patients are referred by telephone or email to the sarcoma coordinator early on clinical grounds. Further imaging studies can then be obtained expeditiously using protocols designed for the diagnosis and management of bone and soft tissue tumours. Tissue diagnosis can then be acquired via an approach designed not to complicate further surgical management.	Descriptive statistics only. Errors bars displayed but not labelled. Data displayed graphically but corresponding figures are not supplied, data cannot be fully extracted. The study reports referral delay is a problem in sarcoma. No evidence linking referral delay to prognosis is given.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Goyal *et al.* (2004)	To analyse the influence of the component parts of symptom interval for young people with bone tumours. To examine the relationship between symptom interval and survival.	Retrospective case series.	103 patients (aged 4–22 years) presenting to a single institution between 1990 and 1992 with osteosarcoma (n=68) or Ewing's sarcoma (n=35). UK	Overall and event-free survival, symptom interval and the component parts of the symptom interval (lag between symptoms and definitive diagnosis & treatment).	50% of patients initially presented to their GP, 36% to A&E, 5% directly to a consultant and 2% to other health professionals. In 77 cases the action of the first clinician was recorded. These actions were: Imaging studies (61%), antibiotics or analgesics prescribed (23%), and immediate referral to another professional (14%). Symptom interval (SI): The median total SI was 3.8 months (range 1–46 months). For osteosarcoma median SI was 3.4 months (range 1–15 months). For Ewing's sarcoma median SI was 5.7 months (range 1–46 months). Patient age >12 years old was associated with increased SI (p=0.05). Axial site of tumour was associated with increased professional delay (p<0.01). For Ewing's sarcoma professional delays were significantly longer when presenting to a GP than to A&E (p=0.02) with, but not for osteosarcoma. No difference was found between the overall and event-free survival of patients grouped by SI (<3months, 3-6 months or >6months) when both tumours were grouped together or when analysed separately. Presentation to A&E more commonly led to immediate X-rays than with a GP consultation. The overall likelihood of being X-rayed was similar whether presenting to GP (46%) or A&E (51%), although the time required (and hence delay) was much shorter for A&E. Authors' conclusions: Early referral to specialists would help to alleviate anxiety and distress to the patient and family, even if currently, delay does not influence outcome.	A patient was considered symptomatic from the date that symptoms attributable to the bone tumour were first recorded. This definition could underestimate patient related delay, especially given the young age of many of the patients. The survival analysis did not include other known prognostic factors. The length of follow up was not reported. The event rate is not reported in the survival analysis. Incomplete reporting of survival analysis.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Widhe & Widhe (2000)	To establish the initial symptoms and physical signs of osteosarcoma and Ewing's sarcoma, and to identify early characteristics of the disease to shorten the delay in diagnosis.	Population based case series.	All patients less than 30 years old diagnosed with osteosarcoma (n=102) and Ewing's sarcoma (n=47) in Sweden between 1983 and 1995. Tumours in the skull or ribs were excluded. SWEDEN	Presenting symptoms and signs; initial diagnosis, patient related diagnostic delay, and doctor related diagnostic delay.	Patient delay was defined as time from symptoms to initial medical visit. Doctor delay was time from initial visit to accurate diagnosis. For osteosarcoma average patient related delay was 1.5 months (range 0.2 to 6.5) and doctor related delay was 2.3 months (range 0.2 to 12). For Ewing's sarcoma average patient related delay was 3.8 months (range 0.2 to 20) and doctor related delay was 4.8 months (range 0.2 to 18). Shorter doctor's delay was associated with three factors; the presence of a palpable mass, the ordering of a radiograph, and the age of the patient (children having a shorter delay). 68 (67%) of the patients with osteosarcoma and 28 (60%) of those with Ewing's sarcoma had a radiograph made at the first medical visit. The correct diagnosis was not established for all patients who had an X-ray: The radiograph was misinterpreted as inconclusive or normal for 6 (9%) of the patients with osteosarcoma and for 12 (43%) of the patients with Ewing sarcoma.	Authors comment that the patient-related delay may be impossible to change the only way to reduce total delay is to shorten the doctor's delay.	3+
Wurtz *et al.* (1999)	To evaluate the duration, frequency and implications of delays in the treatment of primary pelvic bone sarcomas.	Case series.	68 patients with primary bone sarcoma of the pelvic girdle diagnosed and treated at a single orthopaedic surgery department between 1975 and 1995. USA	Prognostic factors for survival (tumour histologic diagnosis, grade, size and site; patient sex, duration of symptoms and delay in diagnosis). Inappropriate treatment.	Average duration of symptoms before accurate diagnosis was 10 months (range 1 month to 4 years). 2 patients were asymptomatic. 30/68 (44%) patients experienced a diagnostic delay of more than 1 month after their first physician visit for evaluation of symptoms. The average doctor-related diagnostic delay for these 30 patients was 7 months (range 1 month to 3 years). Pre-referral imaging: Pelvic sarcoma was discovered as an abnormality on an initial radiograph in 49/68 (72%) of patients.	Small study, only 30 patients included in the survival analysis. The pelvic sarcoma was discovered on an initial anteroposterior plain radiograph of the pelvis in 49/68 (72%) of patients before any other imaging was made. Authors comment on the difficulty in radiographic recognition of bone tumours of the pelvis.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Survival analysis: Median follow up was 4 years. Univariate analysis revealed female gender, histological diagnosis, and tumour grade as prognostic factors (all p<0.01). Multivariate analysis (Cox regression) showed female gender and low tumour grade as favourable prognostic factors (p<0.01). No significant association between duration of symptoms and survival was detected (p=0.54). No significant association between diagnostic delay and survival was detected (p=0.62), using a range of delays to divide the patient group. Authors' conclusions: Patients who have a primary bone sarcoma of the pelvis often have symptoms for a long duration that mimic those of more commonly encountered non-neoplastic conditions. If symptoms are out of the ordinary physicians should order and carefully examine a high quality radiograph of the pelvis.		
Barlow & Newman (1994).	To review the contents of the Leeds Regional Bone Tumour Registry with regard to the shoulder.	Within group comparison.	145 primary bone tumours of the shoulder region in a registry of 2039 cases gathered from 1958–1994. 73 cases were malignant and 72 benign. UK	Tumour site and type, diagnostic accuracy.	Tumour site: Seventy five per cent of tumours occurred in the proximal humerus, 20% in the scapula and 5% in the outer half of the clavicle. Tumour type: 73 cases were malignant and 72 benign. Commonest tumour types were: unicameral cyst 40 cases, osteosarcoma 26 cases and chondrosarcoma 21 cases. Simple bone cyst was the commonest diagnosis in children, chondrosarcoma in the middle age group and osteosarcoma in the over 60s. Diagnostic accuracy: Cases submitted to the register were subject to central diagnostic review. In 13 cases the preoperative diagnosis was deemed incorrect and resulted in suboptimal management. A biopsy was performed before surgery in 82/145 (57%) cases. In the remaining 63/145 (43%) of patients, treatment was undertaken on the basis of clinical findings alone.	Some cases could date back to 1958.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					In 11/145 (8%) of cases the histological diagnosis of the tumour registry differed from the referring pathologist's diagnosis with important clinical implications. In 6/145 (4%) the patient's diagnosis was delayed by failure to order a radiological examination. In 7/145 (5%) patient's diagnosis was delayed by failure to take an adequate biopsy. Authors' conclusions: An adequate biopsy specimen obtained at the time of presentation should be referred to a specialist pathologist or tumour panel for optimal management. Increased awareness of the causes of local symptoms, prompt radiological investigation and expeditious biopsy of suspicious lesions are basic prerequisites for the satisfactory management of these patients.		
Aboulafia *et al.* (2002).	To estimate the appropriateness of pre-referral imaging in patients with bone and soft tissue tumours.	Observational study, prospective case series.	100 consecutive patients referred to an orthopaedic oncology practice. 76 bone tumours: 57 were benign or non-neoplastic, 9 were metastases and 10 primary malignancies. 24 soft tissue tumours: 15 were benign or non-neoplastic, 2 metastases and 7 primary malignancies. USA	Number, cost and appropriateness of imaging studies ordered by referring physicians. Number of physician visits before referral.	Patients were divided into two groups: 1) Those with benign bone tumours and non-neoplastic conditions. 2) Those with malignant soft tissue or bone tumours. Proportion of inappropriate imaging studies: • Group 1: CT 12/22 (55%), MRI 23/41 (56%), and bone scans 16/30 (53%). • Group 2: CT 2/13 (15%), MRI 3/35 (9%) and bone scans 2/12 (17%). Average number of physician visits before referral for benign tumours was 4.04, for non-neoplastic conditions 6.5 and for malignant tumours 4.85 visits. Cost of unnecessary imaging was estimated at $514 per patient.	US study, the organisation of radiological services is unlikely to be applicable to the UK setting. Appropriateness of imaging was judged by consensus of 2 orthopaedic oncologists. Data not analysed statistically. Authors acknowledge that judgement of appropriateness of imaging is subjective. Also the number of patients with benign or non-neoplastic lesions who are not referred is an unknown in this study.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: Early referral to an orthopaedic oncologist will provide a substantial cost saving, especially for those with benign bone lesions and non-neoplastic bone lesions mimicking malignant tumour.		

Table 2.c Diagnosis of sarcomas by specialist radiologist compared with general radiologist.

Abbreviations: CT, computerized tomography; DGH, District General Hospital; MDT, multidisciplinary team; MRI, magnetic resonance imaging; RCR, Royal College of Radiologists; STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Grimer & Sneath (1990)	To highlight problems in the early management and diagnosis of malignant bone tumours.	Case series.	70 patients with malignant bone tumours referred to a single bone tumour treatment centre during 1 year. UK	Patient delay, diagnostic delay, sensitivity of initial X-ray diagnosis, biopsy errors.	Longest diagnostic delays occurred in those whose initial radiographs were erroneously reported as normal (13/70 patients). In this patient group 58% required amputation or were inoperable compared to 15% of patients whose initial radiographs were interpreted correctly. Factors contributing to the tumour being missed on the radiograph were poor quality of the radiograph, and failure to demonstrate the whole of the lesion. Authors' conclusions The radiological signs of tumours are easily overlooked. The suspicion of any of these abnormalities on a radiograph should prompt the clinician to consider the possibility of a sarcoma and to order further investigation.	Specialist centre was NSCAG designated bone tumour treatment service.	3+
Saifuddin *et al.* (2000).	To assess the adequacy of pre-referral MRI.	Case series.	Consecutive MRI examinations and available reports performed on patients prior to referral to a bone and soft tissue tumour unit. The series consisted of 50 patients, referred over a 1 year period, 31 with bone tumours and 19 with soft tissue tumours. Patients were referred from 41 different hospitals.	Technical adequacy of MRI studies, adequacy of MRI reporting.	Technical adequacy: The radiologist at the specialist bone and soft tissue tumour unit estimated that 129 MRI sequences would be needed to characterise the 50 tumours. The actual number of sequences performed was 255 indicating a tendency to perform too many sequences. The commonest mistake was the failure to image the whole bone for skip metastases, in the case of bone tumours. Axial imaging was omitted in 4/50 (8%) of cases.	Unclear how criteria for appropriateness of imaging were decided. Diagnostic accuracy of the referring radiologists is not reported.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
			Reports were available for 40 of these patients. UK		Adequacy of reports: Reporting of the MRI studies was typically incomplete. Information about the precise intraosseous and extraosseous extent of the tumour and its relationship to the neurovascular bundle and adjacent joint was commonly excluded. In 20/26 patients with bone tumours for whom a report was available, a diagnosis or differential diagnosis was included. No reference was made in any of these 20 cases to the plain radiographic appearance of the tumour. Authors' conclusions: This audit indicates that a greater awareness is needed amongst general radiologists of the MR imaging and reporting requirements for musculoskeletal tumours.		
Aboulafia *et al.* (2002).	To estimate the appropriateness of pre-referral imaging in patients with bone and soft tissue tumours.	Prospective case series.	100 consecutive patients referred to an orthopaedic oncology practice. 76 bone tumours: 57 were benign or non-neoplastic, 9 were metastases and 10 primary malignancies. 24 soft tissue tumours: 15 were benign or non-neoplastic, 2 metastases and 7 primary malignancies. USA	Number, cost and appropriateness of imaging studies ordered by referring physicians. Number of physician visits before referral.	Patients were divided into two groups: 1) Those with benign bone tumours and non-neoplastic conditions. 2) Those with malignant soft tissue or bone tumours. Proportion of inappropriate imaging studies: • Group 1: CT 12/22 (55%), MRI 23/41 (56%), and bone scans 16/30 (53%). • Group 2: CT 2/13 (15%), MRI 3/35 (9%) and bone scans 2/12 (17%). Average number of physician visits before referral: • Benign tumours: 4.04 visits	US study; differs from UK setting with large numbers of small (non-specialist) private diagnostic imaging centres. Appropriateness of imaging was judged by consensus of 2 orthopaedic oncologists. Authors acknowledge that judgement of appropriateness of imaging is subjective. Also the number of patients with benign or non-neoplastic lesions who are not referred is an unknown in this study. Data not analysed statistically.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					• Non-neoplastic conditions 6.5 visits • Malignant tumours 4.85 visits. Cost of unnecessary imaging is estimated at $514 per patient. Authors' conclusions: Early referral to an orthopaedic oncologist will provide a substantial cost saving, especially for those with benign bone lesions and non-neoplastic bone lesions mimicking tumour.		
Ashwood *et al.* (2003).	To investigate the sources of delay in diagnosis and determine if there was a similar diagnostic error rate as found by the Musculoskeletal Tumour Society, which subsequently altered patients' management and affected outcome.	Prospective case series.	100 consecutive patients referred to a supra-regional bone and STS service. UK	Delay in referral to the bone tumour unit. Radiograph prior to referral. Inappropriate or inadequate imaging. Biopsy complications.	100 patients overall with 41 benign, 47 sarcoma and 9 metastatic tumours. Average referral delay for each tumour category: • All tumours 13.5 months (range 0–32 months) • Malignant 7.5 months (range 0–13 months) • Metastatic <5 months • Benign >20 months Imaging prior to referral: Plain radiograph: 96/100 (96%). Complex imaging (MRI or CT) 63/100 (63%). 56/63 (89%) of complex imaging studies were inadequate and had to be repeated (contributing to the referral delay). In 7/47 (15%) of cases seeding of tumour was risked by poorly positioned needle (5) and open biopsies (2) that contaminated intra-articular components.	Descriptive statistics only. Errors bars displayed but not labelled. Data displayed graphically but corresponding figures are not supplied, data cannot be fully extracted. The study reports referral delay is a problem in sarcoma. No evidence linking referral delay to prognosis is given.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: Delay in diagnosis may allow the tumour size to increase – a factor associated with poor outcome. Following a plain radiograph, patients are referred by telephone or email to the sarcoma coordinator early on clinical grounds. Further imaging studies can then be obtained expeditiously using protocols designed for the diagnosis and management of bone and soft tissue tumours. Tissue diagnosis can then be acquired via an approach designed not to complicate further surgical management.		
Loughrey *et al.* (1999).	To determine whether specialist oncological review of CT imaging affects patient management.	Within group comparison.	124 patients attending a regional oncology centre over a 1 year period, who had review of cross sectional imaging. Study included 129 (87%) CT studies and 19 (13%) MRI studies. The group were drawn at random from a case series of 526. The most common diagnoses were non-Hodgkin's lymphoma (17%), Hodgkin's disease (11%) and colorectal carcinoma (11%). 8 (6%) patients had sarcoma. UK	Technical adequacy of cross sectional imaging studies. Agreement between outside and review reports.	Technical adequacy: Coverage was deemed adequate in 94% of cases. A calibration rule was absent in 9% of cases. Comparison of outside and review reports: Only 33% of outside reports provided dimensions of measurable disease. Specific comment was made by outside reports on the appearance of the liver, lungs and bones in 77%, 55% and 16% of appropriate cases. A fundamental difference in interpretation arose in 41/122 (34%) of reports. The specialist review upstaged disease in 15 cases, downstaged disease in 6 patients and excluded disease in 2 patients. Additional sites of disease were noted in 8 patients and excluded in 6 patients. In 4 cases of disagreement the independent arbiter agreed with the original (non-specialist) report. Common sites of disagreement were the mediastinum, pelvis, retroperitoneum, axilla and neck. No specific tumour type appeared associated with difficulty in radiological interpretation.	RCR 1994 CT guidelines were considered as national standard practice and used to judge the adequacy of pre-referral imaging. Delayed specialist radiological reviews were of reduced relevance to patient management. Specialist radiologists defined as those based in a regional oncology centre.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Impact on management: Specialist radiological review affected management in 9/122 patients (7%). 4 patients underwent additional investigative procedures and treatment was changed in 5 patients. In 7% of cases the delay between initial cross sectional imaging and specialist review was 6 months; the extent of the patient's disease was likely to have changed and the review findings of limited value. Author's conclusions: Specialist oncological radiology review of outside cross-sectional imaging changed radiological staging in 19% of cases but had little impact on patient management. Oncological cross-sectional imaging techniques in the North West of England are of high quality, probably helped by recent RCR guidelines.		
Glencross *et al.* (2000)	To retrospectively assess the referral patterns, investigation, surgery and outcomes of patients with STS in the Trent region of the UK.	Retrospective case series.	204 patients with STS registered with the Trent Cancer Registry, 1995–1997 were included. A second audit was performed on a smaller group of 40 patients treated in a single cancer centre in 1999. UK	Clinical details, tumour characteristics, presentation, management and follow-up.	Preoperative MRI or CT: Overall 37% of patients initially referred to a DGH or cancer unit had a preoperative MRI or CT scan compared to 51% of those initially referred to a cancer centre (p=0.063). 68% of patients with deep tumours received a preoperative MRI or CT scan. In the second audit of a single cancer centre only 45% of patients received a preoperative MRI or CT scan	A sub-set of the studies results have been considered in this appraisal.	

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors conclusions: The management of STS in this region falls below national and international standards. Improving management will involve raising the awareness of primary care physicians who initiate the referral process, and the implementation of guides. Specialist MDTs should manage these patients.		

Table 2.d Referral delay for people with STS.

Abbreviations: CT, computerised tomography; MRI, magnetic resonance imaging; SSG; Scandinavian Sarcoma Group; STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Aboulafia *et al.* (2002)	To estimate the appropriateness of pre-referral imaging in patients with bone and soft tissue tumours.	Prospective case series.	100 consecutive patients referred to an orthopaedic oncology practice. 76 bone tumours: 57 were benign or non-neoplastic, 9 were metastases and 10 primary malignancies. 24 soft tissue tumours: 15 were benign or non-neoplastic, 2 metastases and 7 primary malignancies. USA	Number, cost and appropriateness of imaging studies ordered by referring physicians. Number of physician visits before referral.	Patients were divided into two groups: 1) Those with benign bone tumours and non-neoplastic conditions. 2) Those with soft tissue and malignant bone tumours. Proportion of inappropriate imaging studies: Group 1: CT 12/22 (55%), MRI 23/41 (56%), and bone scans 16/30 (53%). Group 2: CT 2/13 (15%), MRI 3/35 (9%) and bone scans 2/12 (17%). Average number of physician visits before referral: Benign tumours: 4.04, non-neoplastic conditions 6.5 and malignant tumours 4.85 visits. Cost of unnecessary imaging is estimated at $514 per patient. Authors' conclusions: Early referral to an orthopaedic oncologist will provide a substantial cost saving, especially for those with benign bone lesions and non-neoplastic bone lesions mimicking tumour.		3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Ashwood *et al.* (2003)	To investigate sources of delay in diagnosis of bone and soft tissue tumours and estimate diagnostic error rate.	Prospective case series.	100 consecutive patients referred to a supra-regional bone and STS service. Cases included 23 STS, 24 bone sarcoma, 12 bone metastases, and 41 benign tumours. UK		Mean referral delay: • Malignant tumours 7.5 months • Benign tumours 18.8 months • All tumours13.5 months Range of referral delays: • Malignant tumours 0 to 13 months • Benign tumours 32 months at most • All tumours 0 to 32 months	Descriptive statistics only. Errors bars displayed but not labelled. Data displayed graphically but corresponding figures are not supplied, data cannot be fully extracted. The study reports referral delay is a problem in sarcoma. No evidence linking referral delay to prognosis is given.	3+
Bauer (2004)	Presentation outlining the past 25 years of the Scandinavian Sarcoma Group.	Population based case series.	Patients with STS of the extremity or trunk treated at one of the SSG centres (Karolinska Hospital). 3 time periods are presented: 1986–1990 (116 cases), 1991–1996 (213 cases) and 1997–2002 (256 cases). SWEDEN	5 year local control, 5 year overall survival, tumour size, grade and depth at presentation.	After the dissemination of referral guidelines referrals increased with time (116 in 1986–1990 to 256 in 1997–2002). If the incidence of sarcoma is fixed this suggests that fewer patients are now being inappropriately treated locally. 5 year local control rate: • 1986–1990: 67% • 1991–1996: 82% • 1997–2002: 90% 5 year survival rate: • 1986–1990: 58% • 1991–1996: 73% • 1997–2002: 75% Mean size of tumour at presentation: • 1986–1990: 8cm • 1991–1996: 6cm • 1997–2002: 6cm Proportion of deep seated tumours at presentation: • 1986–1990: 76%	There is an association between better referral and improved patient outcome in this study, but causality cannot be inferred due to the study design. Descriptive statistics only.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					• 1991–1996: 61% • 1997–2002: 61% 79% of tumours were high grade in all 3 time periods. Proportion of deep lesions referred before biopsy or excision: • 1986–1990: 61% • 1997–2002: 80% Author's conclusions: Better referral practices in recent years mean that more tumours are untouched, smaller and less deep seated at presentation. This allows for more complete surgical resection and in turn improves local control and survival.		
Bauer *et al.* (2004)	General discussion of the SSG Register.	Population based case series.	SSG Register of patients treated for bone and soft tissue sarcoma between 1986 and 2001. FINLAND, NORWAY, SWEDEN	Size, depth and grade of STS. Local control and patient survival.	In the SSG register as a whole size, depth and grade of reported STS lesions have not changed greatly over the period 1986–2001. Authors suggest that on the whole good referral practices were already established by 1986. The rate of primary referral before surgery improved from 69% in 1986–1989 to 84% in 1999–2001. A subset of the data (Karolinska Hospital, Sweden) is discussed in detail; the authors attribute its improvement in local control and survival rates (57% to 75%) to improved referral practices leading to more patients with small subcutaneous lesions and better prognosis.	The paper lists the participating centres and number of patients reported and reviews some of the research findings emanating from the SSG. The SSG register is population based (except for FINLAND). Data not analysed statistically. In one institution, better referral practices were associated with an improvement in patient metastasis free survival.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Clark & Thomas (2005)	To measure the duration and source of referral delays to a specialist STS unit.	Prospective case series.	216 patients referred to the STS unit of the Royal Marsden Hospital over 12 month period. UK	Referral delay.	Referral delay was defined as the period of time that elapsed between the patient's initial presentation to their GP and referral to the STS unit. 159 patients had previously untreated STS. 31 patients (19.5%) had delays in referral greater than 3 months. In this delayed group the mean delay was 22 months, median delay 14 months and the range was 4 to 96 months. The major sources of delayed referral were: GP (13 patients), patient (2 patients), hospital or specialist (8 patients) and multi-factorial (9 patients).	Authors comment "A fifth of patients with STS encountered delays in referral to this specialist unit. This duration of delay is likely to have had a detrimental effect on treatment options and outcomes". No data relating to patient outcomes.	3+
Lothian *et al.* (2003)	To describe referral pathways and assess delays in referral in order to target educational initiatives.	Population based case series.	362 patients with sarcoma identified from the Northern & Yorkshire cancer registry, 1999–2000. UK	Proportion of patients referred to specialist sarcoma treatment centre; delay in secondary and tertiary referrals.	No patient was treated at more than 3 hospitals. 225/362 (60%) of patients were eventually referred to a specialist sarcoma treatment centre. Patients referred for specialist treatment tended to be younger than those managed at the initial hospital (median age 55–59 vs. 65–69 years, $p<0.01$). Median duration of symptoms was 292 days for patients referred onwards and 419 for those managed at the initial hospital. Referral delay: Average delay in secondary referral was 52 days (median 34 and range 0–678 days); average delay in tertiary referral was 77 days (median 35 and range 0–414 days).	Conference presentation. Only abstract available.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: Although evidence suggests sarcoma treatment is best accomplished in a sarcoma MDT, less than 60% of patients access such teams. Future guidelines may therefore be usefully targeted at both primary and secondary care.		
Teenage Cancer Trust: unpublished data (2004)	To survey the views of teenagers with cancer on their treatment.	Cross sectional study.	Survey completed by 271 teenagers and young adults with cancer attending a conference. Age range 14–24 yrs. Information about diagnosis was available for 205 people. This group included 43 patients with 'bone-cancer', and 14 with STS. UK		42% of those with STS said they visited their GP more than five times before they were referred to hospital.	Unpublished report. Sample bias, all respondents were conference attendees.	3-

Table 2.e Do delays in diagnosis result in poor outcomes for people with sarcoma?

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computerised tomography; ENT, ear, nose & throat; MRI, magnetic resonance imaging; NSCAG, National Specialist Commissioning Advisory Group; SI, symptom interval; STS, soft tissue sarcoma; UICC, Union Internationale Contre Cancer;

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Bacci *et al.* (1999)	To verify the assumption that delayed diagnosis in Ewing's sarcoma negatively influences prognosis.	Case series.	618 patients with newly diagnosed Ewing's sarcoma of bone seen at a single institution between 1979 and 1997. ITALY	Localised or metastatic disease.	Overall the average time from initial symptoms to final diagnosis was 18 weeks. For patients with localised disease this interval was 19 weeks; for patients with metastatic disease 14 weeks. On average, medical advice was sought 13 weeks after the onset of symptoms; this wait was the major component of diagnostic delay. The interval between clinical onset and the final diagnosis was not associated with tumour stage. Rather, patients with metastatic disease were generally diagnosed more quickly than those with localised disease.	Authors suggest that biological differences in the aggressiveness among sub-groups of Ewing's sarcoma are the reason that patients with metastatic disease were generally diagnosed earlier. Time from initial symptoms to medical advice / diagnosis was retrospectively evaluated. Possible recall bias. The patient pathway from initial symptoms to diagnosis is not described.	3+
Bacci *et al.* (2000)	To investigate the correlation between diagnostic delay and the stage of the tumour at presentation.	Retrospective case series.	965 patients with high-grade osteosarcoma of the extremities diagnosed between 1983 and 1999. ITALY	Data collected: Time of initial signs and symptoms; time of first radiography; time of diagnostic biopsy. Intervals evaluated: Interval from initial symptoms to first medical advice; interval from first medical advice to first radiography; interval from first radiography to diagnostic biopsy.	Mean interval between onset of first symptoms and the final diagnosis was significantly shorter in patients with metastatic disease (4 weeks, range 3 to 29) than in patients with localised disease at the time of diagnosis (6 weeks, range 0 to 29). The difference was due to late presentation of patients with localised disease to the physician and not to delays in performing radiological examinations or in referring patients to a specialist hospital for biopsy and treatment. Authors conclude that in high-grade osteosarcoma of the extremity the shorter interval between onset of symptoms and diagnosis observed in patients with disseminated disease	Considerable potential for recall biases; documentation biases.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					at the time of the diagnosis reflects a more aggressive behaviour of tumours that are metastatic at presentation.		
Brouns *et al.* (2003)	To determine doctor and patient related delay in diagnosis of STS.	Case series.	100 consecutive patients referred to a sarcoma treatment centre for treatment of primary STS between 1999 and 2001. BELGIUM	Tumour histological type, patient related and doctor related delay in diagnosis.	93/100 patients discovered the tumour themselves. 53/100 patients did not delay in seeking medical advice. The remaining 47 patients waited between 1 and 240 months (median 4 months) before seeking advice. Doctor delay occurred in 27/100 patients, ranging from 2 to 79 months (median 6 months) in duration. The most frequent reason for doctor-related delay was initial misdiagnosis based on clinical examination alone. Delay was analysed by tumour grade. 85% of high grade tumours were diagnosed within 6 months, 50% without delay. Low grade tumours either had no delay (50%) or a delay longer than 6 months (45%).	Authors comment that the putative link between diagnostic delay and prognosis is complicated by tumour grade. Fast growing, high grade tumours may be diagnosed more quickly but have an inherently poorer prognosis. Authors suggest that population education about a growing painless lump is indicated.	3+
Clasby *et al.* (1997)	To determine how, and by which specialties, patients with STS are investigated and treated within a single large health region and with what outcomes and implications for resource uptake.	Retrospective observational study – clinical audit (Population-based study).	377 patients with primary STS in SE Thames Region 1986–92. UK	Presentation, investigation, treatment and outcome (from hospital records) were compared with defined criteria for optimum management.	Median time from first symptom to first hospital appointment was 3 months (range 1 to 39 months). Significant differences were noted between districts for this time interval. The median time between the first hospital appointment and date of first treatment was 3 weeks (range 1 day to 3 months). Survival analysis, adverse prognostic factors: Preoperative duration of tumour (1 year or less), tumour size (more than 10 cm), age, recurrence (none, local or distant), and non-liposarcoma histology.	Larger tumour size and shorter preoperative tumour duration were independent adverse prognostic factors for survival. Original pathological materials were requested for review in a sub-set (23%) of cases. Authors conclude that investigation and management of many patients with STS was both variable and suboptimal. Patients with sarcoma are more appropriately managed in specialist centres.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Durve *et al.* (2004)	To review the presentation, management and outcome of paediatric patients with rhabdomyosarcoma of the ear and temporal bone, presenting to one centre.	Case series.	14 patients with rhabdomyosarcoma of the ear or temporal region. All patients presented to a single centre between 1980 and 2000. Median age at presentation was 4.5 years (range 1–8.6 years). UK	Lag time (symptom interval), survival and morbidity.	Lag time: Delay in diagnosis varied considerably between patients. Mean interval between symptom onset and definitive diagnosis was 21 weeks, range 4–78 weeks. In many patients the presentation mimicked chronic otitis media, delaying diagnosis. Authors report that there was no clear correlation between length of symptoms and disease stage and subsequent outcome. No statistical comparison is reported, however. Survival: The 5 year disease free survival rate was 81% (SE 12%). Authors' conclusions: The patients usually present to an ENT surgeon who should keep the diagnosis in mind when dealing with chronic otitis media as early diagnosis with referral to a specialist MDT will optimize the chance of survival.	Small number of patients included.	3-
Goyal *et al.* (2004)	To analyse the influence of the component parts of symptom interval for young people with bone tumours. To examine the relationship between symptom interval and survival.	Retrospective case series.	103 patients (aged 4–22 years) presenting to a single institution between 1990 and 1992 with osteosarcoma (n=68) or Ewing's sarcoma (n=35). UK	Overall and event-free survival, symptom interval and the component parts of the symptom interval (lag between symptoms and definitive diagnosis & treatment).	50% of patients initially presented to their GP, 36% to A&E, 5% directly to a consultant and 2% to other health professionals. In 77 cases the action of the first clinician was recorded. These actions were: Imaging studies (61%), antibiotics or analgesics prescribed (23%), and immediate referral to another professional (14%). Symptom interval (SI): The median total SI was 3.8 months (range 1–46	A patient was considered symptomatic from the date that symptoms attributable to the bone tumour were first recorded. This definition could underestimate patient related delay, especially given the young age of many of the patients. The survival analysis did not include other known prognostic factors. The length of follow up was not reported. The event rate is not reported in the survival analysis. Incomplete reporting of survival analysis.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					months). For osteosarcoma median SI was 3.4 months (range 1–15 months). For Ewing's sarcoma median SI was 5.7 months (range 1–46 months) Patient age >12 years old was associated with increased SI (p=0.05). Axial site of tumour was associated with increased professional delay (p<0.01). For Ewing's sarcoma, professional delays were significantly longer when presenting to a GP than to A&E (p=0.02) with, but not for osteosarcoma. No difference was found between the overall and event-free survival of patients grouped by SI (<3months, 3–6 months or >6months) when both tumours were grouped together or when analysed separately. Presentation to A&E more commonly led to immediate X-rays than with a GP consultation. The overall likelihood of being X-rayed was similar whether presenting to GP (46%) or A&E (51%), although the time required (and hence delay) was much shorter for A&E. Authors' conclusions: Early referral to specialists would help to alleviate anxiety and distress to the patient and family, even if currently, delay does not influence outcome.		

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Grimer & Sneath (1990)	To highlight problems in the early management and diagnosis of malignant bone tumours.	Case series.	70 patients with malignant bone tumours referred to a single bone tumour treatment centre during 1 year. UK	Patient delay, diagnostic delay, sensitivity of initial X-ray diagnosis, biopsy errors.	Longest diagnostic delays occurred in those whose initial radiographs were erroneously reported as normal (13/70 patients). In this patient group 58% required amputation or were inoperable compared to 15% of patients whose initial radiographs were interpreted correctly. Factors contributing to the tumour being missed on the radiograph were poor quality of the radiograph, and failure to demonstrate the whole of the lesion. Authors' conclusions: The radiological signs of tumours are easily overlooked. The suspicion of any of these abnormalities on a radiograph should prompt the clinician to consider the possibility of a sarcoma and to order further investigation.	Specialist centre was NSCAG designated bone tumour treatment service.	3+
Hussein & Smith (2005)	To investigate the adequacy of current early referral guidelines for extremity STS.	Retrospective case series.	365 people with histologically confirmed STS, who presented to a specialist soft tissue tumour unit. The dates or duration of the case series is not reported. UK	Proportion of patients conforming to each of the NICE referral guidelines for suspected STS. Delays between symptom onset and specialist treatment.	Frequency of guideline features in people presenting with STS: Sub-fascial: 306 (84%) Size > 5cm: 235 (64%) Rapid growth: 214 (57%) Pain: 176 (48%) No guideline features 20 (5%) Delay from onset of symptoms to specialist treatment: Patients with none of the guideline features had an average delay of 33.15 months compared to 19.86 for those with one or more features. 110 patients were seen within 3 months of the onset of their symptoms.		3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Number of patients with guideline features and their average symptom history in months: Features — N — History Deep, rapid, pain, <5cm — 17 — 6.2 Deep, rapid, painless, >5cm — 51 — 6.8 Deep, rapid, pain, >5cm — 92 — 7.1 Deep, painless, slow, <5cm — 20 — 15.5 Superficial, painless, rapid, <5cm — 18 — 19.5 Deep, pain, slow, >5cm — 34 — 31 Deep, painless, slow, >5cm — 44 — 44.6 Deep, pain, slow, <5cm — 22 — 45.1 Authors' conclusions: Patients with STS are experiencing unacceptable delays in referral. Authors argue that the referral guidelines should be modified to emphasise depth, followed by size and history of rapid growth. Simplified referral pathways should reduce delays.		
Muscolo *et al.* (2003)	To report cases of musculoskeletal tumours about the knee misdiagnosed and treated as athletic injuries.	Case series.	25 (4%) of a total 667 patients with tumours about the knee, presenting to a single institution 1980–1998, who had an invasive diagnostic or therapeutic procedure due to a misdiagnosis of athletic injury. Final diagnosis was sarcoma (4 osteosarcoma, 3 chondrosarcoma, 3 fibrosarcoma, 2 Ewing's sarcoma and 1 synovial sarcoma) and benign or intermediate tumour (n=11). ARGENTINA	Change in treatment plan.	Original diagnoses were made on the basis of clinical examination and radiographs alone (no MRI or CT). A more conservative oncological surgical procedure was required following a delay in diagnosis or contamination of the tumour margins in 15/25 patients. Delay in diagnosis: Of the 14 sarcomas, 9 that had been retrospectively judged Enneking stage IIA at initial presentation progressed to stage IIB following delay in diagnosis.	Small sample size. No comparison of outcomes of misdiagnosed patients with the overall group of patients with knee tumours. Case series spanned a period of nearly 20 years.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					The initial invasive diagnostic or therapeutic procedure had contaminated surrounding tissues in 3 of the patients with sarcomas. Authors' conclusions: When a knee tumour is initially misdiagnosed as an athletic injury, treatment may be adversely affected by the delay in diagnosis or an inappropriate invasive procedure. Initial poor quality radiographs and an unquestioned original diagnosis despite persistent symptoms were the most frequent causes of an erroneous diagnosis.		
Pisters *et al.* (1996)	To identify specific independent adverse clinicopathologic factors for event-free survival in a cohort of consecutively treated patients with extremity STS.	Prospective case series.	1041 patients with localised extremity STS treated at a single institution 1982–1994 Patients followed for median 3.95 years. USA	Relationships between patient age, sex and symptoms at presentation, tumour factors and pathologic factors; and end points local recurrence, distant metastasis, disease-specific survival and post-metastasis survival.	Significant independent adverse prognostic factors: For local recurrence: age > 50 years, recurrent disease at presentation, microscopically positive surgical margins, and the histologic subtypes fibrosarcoma and malignant peripheral-nerve tumour. For distant recurrence: intermediate tumour size, high histologic grade, deep location, recurrent disease at presentation, leiomyosarcoma, and non-liposarcoma histology. For disease-specific survival: large tumour size, high grade, deep location, recurrent disease at presentation, the histologic subtypes leiomyosarcoma and malignant peripheral-nerve tumour, microscopically positive surgical margins, and lower extremity site. For post-metastasis survival: only large tumour size (> 10 cm).	Large tumour size was an adverse prognostic factor for: distant recurrence, disease specific survival, and post metastasis survival. Prospective design and large numbers, but patients all from a single centre	3++

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Ramanathan *et al.* (1999).	To evaluate prognostic factors in patients with extremity STS and test the validity of the AJCC and UICC staging system.	Prospective case series.	325 patients with primary untreated STS of the extremities, referred to the Royal Marsden Hospital (1989–1995). Embryonal rhabdomyosarcoma, soft tissue Ewing's sarcoma and primitive neuro-ectodermal tumours (total n=9) were excluded for differences in behaviour and treatment to other extremity STS. UK	Local recurrence, distant metastasis and disease-specific survival.	45 patients had metastatic disease at presentation and were excluded from the analysis. Subject group n = 271. Adverse prognostic factors for distant metastasis were large tumour size and high histological grade. Adverse prognostic factors for disease-specific survival were large tumour size, high histological grade and positive surgical margins. High histological grade was an adverse prognostic factor for local recurrence. Liposarcoma histology tended to be associated with more favourable outcomes.	Also reviews data from 5 similar studies (total n=2115) showing tumour size as an adverse prognostic factor. Concludes that "Histological grade and tumour size are equally important determinants of distant metastases and survival". The authors suggest a modified staging system for STS with equal emphasis on tumour size and grade.	3++
Simpson *et al.* (2005)	To report presenting features, Enneking stage, size of primary tumour, method of treatment and patient and doctor delays in people with Ewing's sarcoma of the upper extremity.	Retrospective case series.	19 patients with Ewing's sarcoma of the upper extremity diagnosed between 1965 and 2005. Patients were identified from the Scottish Bone Tumour registry. Ages ranged from 3 to 57 years, mean of 19 years. UK	Enneking stage, patient and doctor related diagnostic delay, and 10 year disease free survival.	Patient delay and disease stage: Patients with longer delay tended to have higher disease stage (p=0.1, Chi-squared test). Disease free survival: 10 year DFS was 100% for patients with stage IIA disease, 56% for those with stage IIB disease and 0% for those with stage III disease. Authors' conclusions: This study reemphasises the potential importance of a diagnostic delay on outcome.	Small study. All archival pathology was reviewed to confirm diagnosis.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Sneppen & Hansen (1984)	To elucidate the relationship between presenting symptoms and signs and patient-related and doctor-related treatment delay in bone sarcomas.	Case series.	124 consecutive patients with bone sarcoma, 84 with osteosarcoma and 40 Ewing's sarcoma, admitted to a single bone sarcoma treatment centre between 1962 and 1979. DENMARK	Presenting symptoms and signs; patient related delay, doctor related delay, and survival.	Treatment delay (time from initial symptoms to arrival at treatment centre) averaged 6.4 months for osteosarcomas and 9.6 months for Ewing's sarcomas. In both types the delay was relatively short in patients with constant pain and swelling. For osteosarcoma average patient related delay was 1.6 months and doctor-related delay was 1.7 months. For Ewing's sarcoma average patient related delay was 1.5 months and doctor related delay was 6 months. Survival (follow up was between 2 and 10 years) was the same whether the delay was short or long (short and long undefined).	Confidence intervals calculated incorrectly (using standard deviation instead of standard error). Unlikely to affect conclusions. Multiple use of t-test without post-hoc adjustment. Sub-group analysis of delay in high and low grade tumours would have been useful. Paper >20 years old, possibly outdated.	3+
(van Dalen *et al.* 2001)	To analyse the effect of an erroneous diagnosis on the initial treatment of retroperitoneal STS.	Population based case series.	143 patients with primary retroperitoneal STS, confirmed histologically 1989–1994. Patients were identified though the Dutch Network and National Pathology database. Sufficient clinical information was available for 138 patients. Median age was 60 (range 18–88 years). NETHERLANDS	Presenting symptoms and signs, diagnostic imaging and biopsy, accuracy of diagnosis and initial treatment.	138 patients were classified into 2 groups based on the pre-operative diagnosis: correctly diagnosed (n=87) and misdiagnosed (n=51). A palpable mass was seen more often in the correctly diagnosed group than in the misdiagnosed group (69% vs. 43%, p<0.01). Acute abdomen was slight less common in the correctly diagnosed group than in the misdiagnosed group (2% vs. 18%, p<0.01). Median tumour size was larger in the correctly diagnosed group than in the misdiagnosed group (19cm vs. 13cm, p<0.01). Clinical investigations: CT was done more often in the correctly diagnosed group than in the misdiagnosed group (86% vs. 57%, p<0.01). Biopsy was done more often in the correctly	Not reported whether re-resection was attempted in the misdiagnosed group.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					diagnosed group than in the misdiagnosed group (77% vs. 29%, p<0.01). Treatment: Surgery was performed less often in the correctly diagnosed group than in the misdiagnosed group (82% vs. 96%, p<0.01). The discovery of irresecitiblity during surgery was less likely in the correctly diagnosed group than in the misdiagnosed group (1% vs14%, p<0.01). Complete resection was more likely in the correctly diagnosed group than in the misdiagnosed group (57% vs. 51%, p<0.01). If only surgically treated patients are considered, the rate of complete resection was 71% in the correctly diagnosed group and 53% in the misdiagnosed group. Authors' conclusions: More patients with misdiagnosis were unnecessarily operated on for tumours that proved irresectable and fewer of this group could be treated with curative intent, despite the fact that these patients had smaller tumours.		
Widhe & Widhe (2000)	To establish the initial symptoms and physical signs of osteosarcoma and Ewing's sarcoma, and to identify early characteristics of the disease to shorten the delay in diagnosis.	Population based case series.	All patients less than 30 years old diagnosed with osteosarcoma (n=102) and Ewing's sarcoma (n=47) in Sweden between 1983 and 1995. Tumours in the skull or ribs were excluded. SWEDEN	Presenting symptoms and signs; initial diagnosis, patient related diagnostic delay, and doctor related diagnostic delay.	Patient delay was defined as time from symptoms to initial medical visit. Doctor delay was time from initial visit to accurate diagnosis. For osteosarcoma, average patient related delay was 1.5 months (range 0.2 to 6.5) and doctor related delay was 2.3 months (range 0.2 to 12). For Ewing's sarcoma, average patient related delay was 3.8 months (range 0.2 to 20) and doctor related delay was 4.8 months (range 0.2	Authors comment that the patient-related delay may be impossible to change and that the only way to reduce total delay is to shorten the doctor's delay.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					to 18). Shorter doctor's delay was associated with three factors; the presence of a palpable mass, the ordering of a radiograph, and the age of the patient (children having a shorter delay).		
Wurtz *et al.* (1999)	To evaluate the duration, frequency and implications of delays in the treatment of primary pelvic bone sarcomas.	Case series.	68 patients with primary bone sarcoma of the pelvic girdle diagnosed and treated at a single orthopaedic surgery department between 1975 and 1995. USA	Prognostic factors for survival (tumour histologic diagnosis, grade, size and site; patient sex, duration of symptoms and delay in diagnosis). Inappropriate treatment.	Average duration of symptoms before accurate diagnosis was 10 months (range 1 month–4 years). 2 patients were asymptomatic. 30/68 (44%) patients experienced a diagnostic delay of more than 1 month after their first physician visit for evaluation of symptoms. The average doctor-related diagnostic delay for these 30 patients was 7 months (range 1 month to 3 years). Pre-referral imaging: Pelvic sarcoma was discovered as an abnormality on an initial radiograph in 49/68 (72%) of patients. Survival analysis: Median follow up was 4 years. Univariate analysis revealed female gender, histological diagnosis, and tumour grade as prognostic factors (all $p<0.01$). Multivariate analysis (Cox regression) showed female gender and low tumour grade as favourable prognostic factors ($p<0.01$). No significant association between duration of symptoms and survival was detected ($p=0.54$). No significant association between diagnostic delay and survival was detected ($p=0.62$), using a range of delays to divide the patient group.	Small study, only 30 patients included in the survival analysis.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: Patients who have a primary bone sarcoma of the pelvis often have symptoms for a long duration that mimic those of more commonly encountered non-neoplastic conditions. If symptoms are out of the ordinary physicians should order and carefully examine a high quality radiograph of the pelvis.		

Table 2.f Doctor related delay from first medical advice to diagnosis in specialist unit.

Abbreviations: CS, chondrosarcoma; ES, Ewing's sarcoma; OS, osteosarcoma; STS, soft tissue sarcoma.

				Doctor related delay in diagnosis (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Brouns *et al.* (2003)	To determine doctor and patient related delay in diagnosis of STS.	Case series.	100 consecutive patients with primary STS referred to a sarcoma treatment centre for treatment between 1999 and 2001. BELGIUM	More than one month.	27%		6	2 to 79	Authors comment that the putative link between diagnostic delay and prognosis is complicated by tumour grade. Fast growing, high grade tumours may be diagnosed more quickly but have an inherently poorer prognosis. Authors suggest that population education about a growing painless lump is indicated.	3+
Simpson *et al.* (2005)	To report presenting features, Enneking stage, size of primary tumour, method of treatment and patient and doctor delays in people with Ewing's sarcoma of the upper extremity.	Retrospective case series.	19 patients with Ewing's sarcoma of the upper extremity diagnosed between 1965 and 2005. Patients were identified from the Scottish Bone Tumour registry. Ages ranged from 3 to 57 years, mean of 19 years. UK		50% delayed for more than 1 month.		1.25	0.25 to 32	Small study. All archival pathology was reviewed to confirm diagnosis.	3-

				Doctor related delay in diagnosis (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Lawrence, Jr. *et al.* (1987)	To document the clinical presentation, pathology and management of adult soft-tissue sarcomas.	Cross sectional study.	Hospitals with American College of Surgeons approved cancer programs were invited to participate in 2 surveys. Data were obtained from 504 hospitals in 1977–1978 (2355 patients) and 645 institutions in 1983–1984 (3457 patients). USA	More than two months.	50%		2		Response rate for the survey is not reported. Paper possibly outdated.	3+
Bacci *et al.* (1999)	To investigate the correlation between diagnostic delay and the stage of the tumour at presentation.	Retrospective case series.	618 patients with newly diagnosed Ewing's sarcoma of bone seen at a single institution between 1979 and 1997. 482 patients had localised disease and 136 metastatic disease. ITALY	Not stated.	Not reported.	All 1.25 Localised 1.5 Metastatic 0.75			Study does not discuss the referral process. Standard deviations or ranges are not presented for any of the outcomes. The patient pathway from initial symptoms to diagnosis is not described.	3-

				Doctor related delay in diagnosis (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Bacci *et al.* (2000)	To investigate the correlation between diagnostic delay and the stage of the tumour at presentation.	Retrospective case series.	965 patients with primary high-grade osteosarcoma of the extremities diagnosed between 1983 and 1999. ITALY	Not stated.	Not reported.	All 1.2 Localised 1.2 Metastatic 1.3			Considerable potential for recall bias; documentation bias. Authors conclude that in high-grade osteosarcoma of the extremity the shorter interval between onset of symptoms and diagnosis observed in patients with disseminated disease at the time of the diagnosis reflects a more aggressive behaviour of tumours that are metastatic at presentation.	3-
Goyal *et al.* (2004)	To analyse the influence of the component parts of symptom interval for young people with bone tumours. To examine the relationship between symptom interval and survival.	Retrospective case series.	103 patients (aged 4–22 years) presenting to a single institution between 1990 and 1992 with osteosarcoma (n=68) or Ewing's sarcoma (n=35). UK	Not stated.	Not reported.		OS 1.4 ES 1.4	OS 0.2 to 13.6 ES 0.1 to 7.1	Results are for OS or ES of the limb.	3-

				Doctor related delay in diagnosis (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Widhe & Widhe (2000)	To establish the initial symptoms and physical signs of osteosarcoma and Ewing's sarcoma, and to identify early characteristics of the disease to shorten the delay in diagnosis.	Population based case series.	All patients less than 30 years old diagnosed with osteosarcoma (n=102) and Ewing's sarcoma (n=47) in Sweden between 1983 and 1995. Tumours of the skull or ribs were excluded. SWEDEN	Not stated.	Not reported.	OS 2.25 ES 4.75		OS 0.25 to 13 ES 0.25 to 18		3+
Wurtz *et al.* (1999)	To evaluate the duration, frequency and implications of delays in the treatment of primary pelvic bone sarcomas.	Case series.	68 patients with primary bone sarcoma of the pelvic girdle diagnosed and treated at a single orthopaedic surgery department between 1975 and 1995. USA	More than one month.	44%	7		1 to 36	Small study, only 30 patients included in the survival analysis.	3-
Grimer & Sneath (1990)	To highlight problems in the early management and diagnosis of malignant bone tumours.	Case series.	70 patients with malignant bone tumours referred to a single bone tumour treatment centre during 1 year. UK	Not stated.	Not reported.	OS 2 ES 7.75 CS 7.5			Case series is presented in the form of an editorial, so there is minimal reporting of patient characteristics or statistical analysis.	3

Table 2.g Patient related delay in diagnosis of sarcoma.

Abbreviations: CS, chondrosarcoma; ES, Ewing's sarcoma; OS, osteosarcoma; STS, soft tissue sarcoma.

				Patient delay before initial presentation to doctor (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Ashwood *et al.* (2003)	To investigate sources of delay in diagnosis of bone and soft tissue tumours and estimate diagnostic error rate.	Prospective case series.	100 consecutive patients referred to a supra-regional bone and STS service. Cases included 23 STS, 24 bone sarcoma, 12 bone metastases, and 41 benign tumours. UK			Malignant: 7.6 Benign 21.2 All tumours: 14.8		Malignant: 0.5 to 11 All tumours: 0 to 26	Descriptive statistics only. Errors bars displayed but not labelled. Data displayed graphically but corresponding figures are not supplied, data cannot be fully extracted. The study reports that referral delay is a problem in sarcoma. No evidence linking referral delay to prognosis is given.	3+
Brouns *et al.* (2003)	To determine doctor and patient related delay in diagnosis of STS.	Case series.	100 consecutive patients with primary STS referred to a sarcoma treatment centre for treatment between 1999 and 2001. BELGIUM	1 month or more.	47%		4	1 to 240	Authors comment that the putative link between diagnostic delay and prognosis is complicated by tumour grade. Fast growing, high grade tumours may be diagnosed more quickly but have an inherently poorer prognosis. Authors suggest that population education about a growing painless lump is indicated.	3+

				Patient delay before initial presentation to doctor (months)						
Study	**Aims**	**Design**	**Population**	**Definition of delay**	**% Delayed**	**Mean**	**Median**	**Range**	**Comments**	**Level**
Bacci *et al.* (1999)	To investigate the correlation between diagnostic delay and the stage of the tumour at presentation.	Retrospective case series	618 patients with newly diagnosed Ewing's sarcoma of bone seen at a single institution between 1979 and 1997. 482 patients had localised disease and 136 metastatic disease. ITALY			All tumours 3.25 Localised 3.25 Metastatic 2.75			Study does not discuss the referral process. Standard deviations or ranges are not presented for any of the outcomes. Time from initial symptoms to medical advice or diagnosis was retrospectively evaluated. Possible recall bias. The patient pathway from initial symptoms to diagnosis is not described.	3-
Bacci *et al.* (2000)	To investigate the correlation between diagnostic delay and the stage of the tumour at presentation.	Retrospective case series.	965 patients with primary high-grade osteosarcoma of the extremities diagnosed between 1983 and 1999. ITALY			All tumours 1.45 Localised 1.5 Metastatic 1.0			Considerable potential for recall bias; documentation bias. Authors conclude that in high-grade osteosarcoma of the extremity the shorter interval between onset of symptoms and diagnosis observed in patients with disseminated disease at the time of the diagnosis reflects a more aggressive behaviour of tumours that are metastatic at presentation.	3-

				Patient delay before initial presentation to doctor (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Goyal *et al.* (2004)	To analyse the influence of the component parts of symptom interval for young people with bone tumours. To examine the relationship between symptom interval and survival.	Retrospective case series.	103 patients (aged 4–22 years) presenting to a single institution between 1990 and 1992 with osteosarcoma (n=68) or Ewing's sarcoma (n=35). UK				OS 1.0 ES 1.9	OS 0 to 6 ES 0 to 5	Results are for OS or ES of the limb. A patient was considered symptomatic from the date that symptoms attributable to the bone tumour were first recorded. This definition could underestimate patient related delay, especially given the young age of many of the patients.	3-
Hussein & Smith (2005)	To investigate the adequacy of current early referral guidelines for extremity STS.	Retrospective case series.	365 people with histologically confirmed STS, who presented to a specialist soft tissue tumour unit. The dates or duration of the case series is not reported. UK	More than 3 months.	70%	21		1-240	Delay is from the onset of symptoms to initiation of treatment in a specialist centre; a combination of patient and referral delay.	

				Patient delay before initial presentation to doctor (months)						
Study	**Aims**	**Design**	**Population**	**Definition of delay**	**% Delayed**	**Mean**	**Median**	**Range**	**Comments**	**Level**
Simpson *et al.* (2005)	To report presenting features, Enneking stage, size of primary tumour, method of treatment and patient and doctor delays in people with Ewing's sarcoma of the upper extremity.	Retrospective case series.	19 patients with Ewing's sarcoma of the upper extremity diagnosed between 1965 and 2005. Patients were identified from the Scottish Bone Tumour registry. Ages ranged from 3 to 57 years, mean of 19 years. UK				6	1 to 180	Small study.	3-
Sneppen & Hansen (1984)	To investigate the relationship between presenting symptoms and signs and patient-related and doctor-related treatment delay in bone sarcomas.	Retrospective case series.	124 consecutive patients with bone sarcoma, 84 with osteosarcoma and 40 with Ewing's sarcoma, admitted to a single bone sarcoma treatment centre between 1962 and 1979. DENMARK			OS 1.6 ES 1.5			Confidence intervals calculated incorrectly (using standard deviation instead of standard error). Unlikely to affect conclusions. Multiple use of t-test without post-hoc adjustment. Sub-group analysis of delay in high and low grade tumours would have been useful.	3+

				Patient delay before initial presentation to doctor (months)						
Study	**Aims**	**Design**	**Population**	**Definition of delay**	**% Delayed**	**Mean**	**Median**	**Range**	**Comments**	**Level**
(van Dalen 2000)	Thesis reporting the management of retroperitoneal sarcoma.	Population based case series.	143 patients with primary retroperitoneal STS, confirmed histologically 1989–1994. Patients were identified though the Dutch Network and National Pathology database. Sufficient clinical information was available for 138 patients. Median age was 60 (range 18-88 years). NETHERLANDS	6 months or more.	41%					3+
Widhe & Widhe (2000)	To establish the initial symptoms and physical signs of osteosarcoma and Ewing's sarcoma, and to identify early characteristics of the disease to shorten the delay in diagnosis.	Population based case series.	All patients less than 30 years old diagnosed with osteosarcoma (n=102) and Ewing's sarcoma (n=47) in Sweden between 1983 and 1995. Tumours of the skull or ribs were excluded. SWEDEN			OS 1.5 ES 3.75		OS 0.25 to 6.5 ES 0.25 to 25	Authors comment that the patient-related delay may be impossible to change; the only way to reduce total delay is to shorten the doctor's delay.	3+

				Patient delay before initial presentation to doctor (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Wurtz *et al.* (1999)	To evaluate the duration, frequency and implications of delays in the treatment of primary pelvic bone sarcomas.	Case series.	68 patients with primary bone sarcoma of the pelvic girdle diagnosed and treated at a single orthopaedic surgery department between 1975 and 1995. USA			3			Small study, only 30 patients included in the survival analysis.	3-
Bergh *et al.* (2001)	To assess the outcome of patients with pelvic, sacral or spinal chondrosarcoma treated at a tumour centre using modern, aggressive surgical techniques and to identify prognostic factors.	Case series.	Sixty nine consecutive patients with chondrosarcoma of the pelvis (46 cases), sacrum (11 cases), and mobile spine (12 cases) who were treated at a University Hospital Musculoskeletal tumour centre from 1967 to 1999. SWEDEN			19.2		6 to 120	Some of the cases reported were treated more than 30 years ago. Specialist centre not explicitly defined, authors refer to "a tumour centre with expertise in the treatment of bone and soft tissue tumours". Inadequate event rate (too few deaths and recurrences) for the number of variables in the multivariate analysis.	3+

				Patient delay before initial presentation to doctor (months)						
Study	***Aims***	***Design***	***Population***	***Definition of delay***	***% Delayed***	***Mean***	***Median***	***Range***	***Comments***	***Level***
Grimer & Sneath (1990)	To highlight problems in the early management and diagnosis of malignant bone tumours.	Case series.	70 patients with malignant bone tumours referred to a single bone tumour treatment centre during 1 year. UK			OS 1.5 ES 4 CS 5.25			Case series is presented in the form of an editorial, so there is minimal reporting of patient characteristics or statistical analysis.	3
Lothian *et al.* (2003)	To describe referral pathways and assess delays in referral in order to target educational initiatives.	Population based case series.	362 patients with sarcoma identified from the Northern & Yorkshire cancer registry, 1999–2000. UK				9.7 for patients referred onwards. 14 for those managed at the initial hospital.		Conference presentation, only abstract available. Unclear whether patients were newly diagnosed or recurrent.	3-
Clasby *et al.* (1997)	To determine how, and by which specialties, patients with STS are investigated and treated within a single large health region and with what outcomes and implications for resource uptake.	Population based case series.	377 patients with primary STS in SE Thames Region 1986–1992. UK				3	1 to 39	Reported delay is from symptom onset to first hospital appointment, cannot separate patient from doctor related referral delay.	3+

Table 2.h Are current guidelines for early diagnosis resulting in improved outcomes?

Abbreviations: CT, computed tomography; MDT, multidisciplinary team; MRI, magnetic resonance imaging; RR, relative risk; SSG, Scandinavian Sarcoma Group; STS, soft tissue sarcoma; US, ultrasound.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Hussein & Smith (2005)	To investigate the adequacy of current early referral guidelines for extremity STS.	Retrospective case series	365 people with histologically confirmed STS, who presented to a specialist soft tissue tumour unit. The dates or duration of the case series is not reported. UK	Proportion of patients conforming to each of the NICE referral guidelines for suspected STS. Delays between symptom onset and specialist treatment.	Frequency of guideline features in people presenting with STS: Sub-fascial: 306 (84%) Size > 5cm: 235 (64%) Rapid growth: 214 (57%) Pain: 176 (48%) No guideline features: 20 (5%) Delay from onset of symptoms to specialist treatment: Patients with none of the guideline features had an average delay of 33.15 months compared to 19.86 for those with one or more features. 110 patients were seen within 3 months of the onset of their symptoms. Authors' conclusions: Patients with STS are experiencing unacceptable delays in referral. Authors argue that the referral guidelines should be modified to emphasise depth, followed by size and history of rapid growth.		3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Nijhuis *et al.* (2001)	To analyse of how well national diagnostic guidelines for STS are being used in one region of Holland.	Retrospective case series.	351 STS patients 1989–1996. Exclusions: gastro-intestinal STS, urogenital STS, paediatric STS, Kaposi sarcoma. Patients were identified from a population based registry. NETHERLANDS	Adherence to diagnostic and referral guidelines. Adequacy of biopsy vs. case volume.	Guidelines were revised in 1994; this study compares 2 periods: 1989–1993 (pre-revision) and 1994–1996 (post-revision). Imaging: In 1989–1993 83% of patients treated at sarcoma treatment centres had at least US or CT of the tumour region compared to 100% of patients in 1994–1996. Adherence to guidelines was significantly better in specialist centres. In district hospitals, patient volume had no significant influence on compliance with guidelines, except for management of patients with STS >3cm. Comparison of conformity to biopsy guidelines (specialist treatment centre vs. all other centres): 32/50 vs. 53/183 (64% vs. 29%). In district hospitals, where fewer than 15 patients were treated in 7 years, significantly more often an inadequate biopsy procedure or even no biopsy was performed prior to resection. Older patients (>60 years) were significantly less likely to be referred to a specialist centre. Authors' conclusions: In many aspects of the diagnostic process of STS, existing guidelines were not followed, especially in community hospitals. Adherence to all individual guidelines was significantly better in the specialised centre. Concentration of patients with STS in a limited number of hospitals and intensified collaboration with specialised centres seem advisable.	Authors state that the guidelines have not been shown to improve patient outcome, but are expected to improve outcome by expert consensus. The quality control and dissemination of the guidelines were, by the authors' admission, inadequate, limiting guideline effectiveness.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Ray-Coquard *et al.* (2004)	To assess the conformity of medical practice to clinical guidelines for the management of patients with STS	Retrospective case series.	100 newly diagnosed STS patients seen during the period 1999–2001. Cases were drawn at random from a series of 650 in a single French region. Exclusions: tumours of bone, CNS and Kaposi sarcoma; metastases at diagnosis. FRANCE	Local and distant recurrence; resection margin. Conformity of management with clinical practice guidelines.	7% of cases had MDT review before biopsy and there were 42% pre-surgery biopsies. Conformity to guidelines was rated 52%, 81%, 94% and 95% for initial surgery, radiation therapy, chemotherapy and follow up respectively R0 resections were more likely (15/35 vs. 10/60 43% vs. 17%, RR: 2.53) and R2 resections less likely (7/35 vs. 36/60, 20% vs. 60%, RR: 0.33) if patients had an MDT evaluation before surgery. R2 resections were less likely in University or cancer hospitals than in general hospitals (27% vs. 61%, RR: 0.44, p=0.02) At multivariate analysis, pre-surgery MDT discussion, management in specialist centre and management within cancer network independently predicted conformity to guidelines. Local relapse was more likely if surgery was performed by a non-specialist (RR:7.33, p=0.02). Local and distant recurrence were more likely if management was outside a specialist centre (RR: 2.33 p=0.02; RR: 1.77 p=0.01) and/or outside a cancer network (RR: 2.32, p=0.02; RR: 1.87 p=0.04). Local recurrence was less likely if a patient was evaluated by an MDT before surgery (RR: 0.52, p=0.02). Distant recurrence was more likely to occur in patients evaluated by an MDT after surgery (RR: 1.64, p=0.04). Authors' conclusions: The development of a treatment strategy within a formal multidisciplinary staff and treatment within a cancer network are both important prognostic factors for optimal clinical care.	Authors' note that dissemination of the national guidelines was deficient. MDTs consisted of weekly meetings of at least one radiologist, pathologist, surgeon, medical oncologist and clinical oncologist. 2 specialist centres were identified in this study: a university hospital and a comprehensive cancer centre. Mean or median follow up not reported but follow up was in the range 8–20 months for survivors. This is unlikely to be long enough to capture the majority of recurrences.	3++

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Lewis *et al.* (2005)	To carry out a systematic review of audits undertaken to assess the implementation and effectiveness of the two week waiting time policy for cancer referrals.	Systematic review.	Clinical audits evaluating cancer referral in the UK. 11 studies examined multiple cancer sites but reported sarcoma results separately. The number of patients with sarcoma in each study ranged from 1 to 11. 8 audits were conducted by a general hospital, 1 by a teaching hospital and 2 by a primary care trust.	Waiting time to first appointment, GP conformity to guidelines, appropriateness of referral and cancer detection rates.	Waiting time to first appointment (2 audits): The proportion seen within 2 weeks was 3/5 (60%) in one study and 8/8 (100%) in the other. GP guideline conformity (6 audits): The number of referrals that met the guidelines ranged from 3/5 (60%) to 100%. Appropriateness of referral (4 audits): The proportion considered to be appropriate ranged from 2/3 (67%) to 4/4 (100%). Authors' conclusions: The proportion of 2 week wait referrals that were found to be in accordance with the guidelines ranged from 60%–100%. The proportion of patients referred via the 2 week wait system and subsequently diagnosed with cancer ranged from 0% to 20%. The proportion of 2 week wait referrals deemed to be appropriate by the hospital clinician ranged from 67% to 100%.	All results were based on audits of 11 patients or less.	2+
Bauer (2004)	Presentation outlining the past 25 years of the Scandinavian Sarcoma Group.	Population based case series.	Patients with STS of the extremity or trunk treated at one of the SSG centres (Karolinska Hospital). 3 time periods are presented: 1986–1990 (116 cases), 1991–1996 (213 cases) and 1997–2002 (256 cases). SWEDEN	5 year local control, 5 year overall survival, tumour size, grade and depth at presentation.	After the dissemination of referral guidelines referrals increased with time (116 in 1986–1990 to 256 in 1997–2002). If the incidence of sarcoma is fixed this suggests that fewer patients are now being inappropriately treated locally. 5 year local control rate: • 1986–1990: 67% • 1991–1996: 82% • 1997–2002: 90%	There is an association between better referral and improved patient outcome in this study, but causality cannot be inferred due to the study design. Descriptive statistics only.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					5 year survival rate: • 1986–1990: 58% • 1991–1996: 73% • 1997–2002: 75% Mean size of tumour at presentation: • 1986–1990: 8cm • 1991–1996: 6cm • 1997–2002: 6cm Proportion of deep seated tumours at presentation • 1986–1990: 76% • 1991–1996: 61% • 1997–2002: 61% 79% of tumours were high grade in all 3 time periods. Proportion of deep lesions referred before biopsy or excision: • 1986–1990: 61% • 1997–2002: 80% Author's conclusions: Better referral practices in recent years mean that more tumours are untouched, smaller and less deep seated at presentation. This allows for more complete surgical resection and in turn improves local control and survival.		

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Bauer *et al.* (2004)	General discussion of the SSG Register.	Population based case series.	SSG Register of patients treated for bone and soft tissue sarcoma between 1986 and 2001. FINLAND, NORWAY, SWEDEN	Size, depth and grade of STS. Local control and patient survival.	In the SSG register as a whole, size, depth and grade of reported STS lesions have not changed greatly over the period 1986–2001. Authors suggest that on the whole, good referral practices were already established by 1986. The rate of primary referral before surgery improved from 69% in 1986–1989 to 84% in 1999–2001. A subset of the data (Karolinska Hospital, Sweden) is discussed in detail; the authors attribute its improvement in local control and survival rates (57% to 75%) to improved referral practices leading to more patients with small subcutaneous lesions and better prognosis.	The paper lists the participating centres and number of patients reported and reviews some of the research findings emanating from the SSG. The SSG register is population based (except for FINLAND). Data not analysed statistically. In one institution, better referral practices were associated with an improvement in patient metastasis free survival.	3-
Rydholm (1997)	To report the experience of a treatment centre for musculoskeletal tumours and impact on referral patterns of the introduction of referral guidelines.	Review article.	Patients referred to SSG treatment centres since 1970. Also epidemiological studies using population based cancer registries. SWEDEN		Description of how local guidelines for the referral of suspected STS were developed using epidemiological data in order to capture most STS at the specialist centre before surgery. Following implementation of referral guidelines, during 1990–1994 four fifths of patients with deep-seated STS were referred before surgery. Guidelines were disseminated though medical schools, referring hospitals and feedback to referring physicians. Author's conclusions: A rapid and reliable way in which to reduce the morbidity of STS would be to increase the number of patients referred to treatment centres before surgery.		4+

Pathology

The questions

a) Does diagnosis by a specialist sarcoma pathologist compared with a general pathologist of sarcomas lead to greater diagnostic accuracy?

b) What is the clinical utility of cytogenetic testing and molecular pathology in people with sarcoma?

Nature of the evidence

a) Does diagnosis by a specialist sarcoma pathologist compared with a general pathologist of sarcomas lead to greater diagnostic accuracy?

16 case series examined expert pathological review and diagnostic accuracy in sarcoma. Four of the studies included people with bone sarcomas only (Barlow & Newman 1994; Remagen 1992; Souhami *et al.* 1997; Stiller *et al.* 2000), seven studies included people with STS only (Alvegard & Berg 1989; Arbiser *et al.* 2001; Coindre *et al.* 1986; Meis-Kindblom *et al.* 1999; Randall *et al.* 2004; Tetu *et al.* 1984; van Dalen 2000) and five included people with either bone or soft tissue sarcoma (Grimer *et al.* 2001; Harris *et al.* 1991; Presant *et al.* 1986; Shiraki *et al.* 1989; Mankin *et al.* 1996).

Diagnostic accuracy was determined in a number of ways, by comparing the diagnoses of: a panel of pathologists versus an individual pathologist (Harris *et al.* 1991; Presant *et al.* 1986; Shiraki *et al.* 1989), an expert pathologist versus an unspecified pathologist (Arbiser *et al.* 2001; Grimer *et al.* 2001), or an expert panel of pathologists versus an unspecified pathologist (Alvegard & Berg 1989; Coindre *et al.* 1986; Meis-Kindblom *et al.* 1999; Tetu *et al.* 1984; van Dalen 2000). Other studies reported histopathological review of non-tertiary diagnoses by a tertiary sarcoma service (Randall *et al.* 2004), of diagnoses recorded at cancer registries (Barlow & Newman 1994; Remagen 1992; Stiller *et al.* 2000), or of patients enrolled in a clinical trial (Souhami *et al.* 1997). One study reported a comparison of biopsy diagnoses and definitive diagnoses in specialist and non-specialist centres (Mankin *et al.* 1996).

Most studies did not define expert or specialist pathologist. The diagnostic accuracy of the expert pathologists was not assessed, but was assumed to be the gold standard, and the expert pathologist was assumed to be correct in any disagreement in diagnosis.

b) What is the clinical utility of cytogenetic testing and molecular pathology in people with sarcoma?

No studies were identified which compared outcomes in people who received genetic testing with those who did not. Two position papers by European (Hogendoorn *et al.* 2004a) and US (Borden *et al.* 2003) expert sarcoma pathologists reported consensus about the clinical utility of such techniques in the diagnosis of sarcoma.

A number of case series analysed the outcomes of patients according to type of fusion gene in synovial sarcoma, Ewing's sarcoma or myxoid liposarcoma, or according to the type of *KIT* mutation in GIST.

Summary of the supporting evidence for the recommendations

a) Does diagnosis by a specialist sarcoma pathologist compared with a general pathologist of sarcomas lead to greater diagnostic accuracy?

There is consistent observational evidence that a histopathological diagnosis of sarcoma is often changed on review by an expert pathologist.

Reports of the rate at which a diagnosis of sarcoma is changed to non-sarcoma on expert review ranged from 3% to 22% of cases (Alvegard & Berg 1989; Arbiser *et al.* 2001; Harris *et al.* 1991; Meis-Kindblom *et al.* 1999; Presant *et al.* 1986; Randall *et al.* 2004; Remagen 1992; Shiraki *et al.* 1989; van Dalen 2000).

Reports of the rate at which the subtype of sarcoma was changed on expert review varied between 16% and 39% of cases (van Dalen 2000; Tetu *et al.* 1984; Shiraki *et al.* 1989; Remagen 1992; Randall *et al.* 2004; Presant *et al.* 1986; Meis-Kindblom *et al.* 1999; Harris *et al.* 1991; Coindre *et al.* 1986; Alvegard & Berg 1989).

Six studies (Alvegard & Berg 1989; Coindre *et al.* 1986; Meis-Kindblom *et al.* 1999; Presant *et al.* 1986; Randall *et al.* 2004; van Dalen 2000) recorded how often the expert pathologist or pathologists disagreed with the tumour grade recorded in the original histopathological report; estimates ranged from 24% to 40%.

A study of diagnosis made on the basis of biopsy (Mankin *et al.* 1996) reported a lower diagnostic error rate, as compared to the definitive diagnosis, at musculoskeletal treatment centres (13%) than at referring institutions (24%). Central histopathological review as part of the European Osteosarcoma Intergroup clinical trial found 2% of the people randomised to participate were in fact ineligible due to incorrect pathology (Souhami *et al.* 1997).

b) What is the clinical utility of cytogenetic testing and molecular pathology in people with sarcoma?

Consensus statements by expert sarcoma pathologists in Europe (Hogendoorn *et al.* 2004a) and America (Borden *et al.* 2003) accept the clinical usefulness of data from genetic tests. They suggest that such testing is likely to be mandatory in the diagnosis of certain types of sarcoma and should be available in all specialist centres. The consensus papers (Borden *et al.* 2003; Hogendoorn *et al.* 2004b) cite observational evidence reporting specific genetic alterations in some histological types of sarcoma. This is of clinical relevance in the sarcomas that are difficult to diagnose histologically but where therapy depends on the tumour type.

Observational studies suggest that fusion gene type is a prognostic marker in Ewing's sarcoma (de Alava *et al.* 1998; Riley *et al.* 2003), and in synovial sarcoma (Kawai *et al.* 1998; Ladanyi *et al.* 2002; Nilsson *et al.* 1999) but did not predict outcome in a series of patients with myxoid liposarcoma (Antonescu *et al.* 2001). There is observational evidence that analysis of KIT mutation may provide prognostic information for people with GIST (Antonescu *et al.* 2003; Kim *et al.* 2004; Singer *et al.* 2002) and predict response to imatinib therapy (Debiec-Rychter *et al.* 2004; Heinrich *et al.* 2003).

Table 3.a Does diagnosis by a specialist sarcoma pathologist compared with a general pathologist of sarcomas lead to greater diagnostic accuracy?

Abbreviations: MDT, multidisciplinary team; MFH, multiple fibrous histiocytoma; RR, relative risk; SSG, Scandinavian Sarcoma Group; STS, soft tissue sarcoma.

					Diagnosis changed on review				
Study	***Aims***	***Design***	***Population***	***Outcomes***	***To non sarcoma***	***Sarcoma subtype***	***Grade***	***Comments***	***Level***
Alvegard & Berg (1989)	To report on a histopathologic peer review performed by an expert pathology committee of all specimens from patients with a primary STS, entered into an adjuvant chemotherapy multicentre trial.	Retrospective case series.	240 patients with primary high grade STS diagnosed 1981–1986. Comparison was between individual SSG pathologists and expert pathology committee. SWEDEN	Agreement on histologic type and grade.	5%	20%	40%	Pathological review panel was not blind to initial diagnosis. Only patients originally diagnosed with STS were included. Patients with suspected STS ruled out by the original pathologist, were not included. Thus the false negative rate cannot be estimated.	3+
Arbiser *et al.* (2001)	To review soft tissue lesions referred for expert consultation to determine types of lesions and/or situations in which major discrepancies occur.	Case series.	266 soft tissue lesions sent to a Soft Tissue Consultation Service Comparison was between referring (non-expert) pathologists and an expert STS pathologist. USA	Agreement on general diagnosis and grade of tumour.	11%	-	-	Authors' conclusions: The lack of familiarity with many rare soft tissue lesions and their variations is probably a more important factor in explaining diagnostic discrepancies than is the increasing use of needle biopsy or the failure to perform sufficient immunohistochemical analysis. The study does not report of the accuracy of diagnosing sarcoma sub-types. The expert pathologist was not blind to the original diagnosis. Cases sent for second opinion are likely to represent a sub-set of diagnostically difficult soft tissue lesions.	3+

					Diagnosis changed on review				
Study	**Aims**	**Design**	**Population**	**Outcomes**	**To non sarcoma**	**Sarcoma subtype**	**Grade**	**Comments**	**Level**
Coindre *et al.* (1986)	To test the reproducibility of a histopathologic grading system using the evaluation of tumour differentiation, mitosis count, and tumour necrosis.	Case series.	Pathologic sections of 25 STS. Comparison between individual pathologists (n=15) and an expert panel. FRANCE	Agreement on histologic type and grade (based on tumour necrosis, differentiation and mitosis count).	-	39%	25%	Authors' conclusions: The tumour grading system outlined in this study provides reliable prognostic information. Relatively low number of tumours included. No benign tumours were included.	3+
Harris & Hartley (1997)	To review the histopathological diagnoses of all sarcomas diagnosed in North West England.	Retrospective population – based case series.	413 of the 450 cases originally registered as sarcomas (bone, STS and visceral) with the Regional Cancer Registry 1982–1984. Comparison was between original pathologist and a panel of 5 pathologists. UK	Agreement on general diagnosis and grade of tumour.	22%	39%	-	Authors' conclusions: Second opinion is essential in cases of presumed sarcomas for studies of incidence and aetiology and to ensure that appropriate treatment is selected. High level of reclassification – could be because this was a population-based series – other similar studies showing lower rates have been on series referred for trials of adjuvant therapy, or specialist institution only. Immunohistochemistry was used in the pathological review, unclear whether it was used for the original pathological reports (1982–1984). No information about the clinical significance of misclassification No data on sarcoma cases missed, but misdiagnosed as something else.	3+

					Diagnosis changed on review				
Study	**Aims**	**Design**	**Population**	**Outcomes**	**To non sarcoma**	**Sarcoma subtype**	**Grade**	**Comments**	**Level**
Meis-Kindblom *et al.* (1999)	To re-evaluate and reclassify cases within the Scandinavian Sarcoma Group (SSG) register.	Retrospective case series.	1000 STS entered into the SSG register between 1986 and 1998. Comparison was between original pathologist and an expert peer review committee of 10–11 pathologists. SWEDEN, NORWAY, FINLAND, DENMARK	Agreement on histologic type and grade.	5%	20%	25%	Authors' conclusions: Pathological review is essential for prognostic studies. An MDT approach to diagnosis is essential. Guidelines for the handling of surgical specimens and reporting should improve diagnosis. Only sarcomas entered onto the SSG register were included. Sarcomas misdiagnosed and not entered were therefore excluded. Misdiagnosis rate is therefore underestimated.	3+
Presant *et al.* (1986)	To review the histopathologic diagnoses of patients with soft-tissue or bone sarcomas on South-eastern Cancer Study Group protocols.	Retrospective case series.	216 consecutive patients with soft-tissue or bone sarcomas admitted to trials between 1972 and 1982. Comparison was between original histopathologic diagnosis and a review by a panel of 3 pathologists. USA	Agreement on histologic type and grade.	6%	34%	24%	Authors' conclusions: Histologic peer review is important in sarcoma studies and is essential in many patients with presumed sarcomas. Some cases date back to 1972, outdated immunohistochemical techniques and diagnostic criteria? Only sarcomas entered onto clinical trials were included. Sarcomas misdiagnosed and not entered were therefore excluded. Misdiagnosis rate is therefore underestimated.	3-

					Diagnosis changed on review				
Study	**Aims**	**Design**	**Population**	**Outcomes**	**To non sarcoma**	**Sarcoma subtype**	**Grade**	**Comments**	**Level**
Shiraki *et al.* (1989)	To evaluate histologically by a panel of pathologists from member institutions, tumours entered in the Eastern Cooperative Oncology Group (ECOG) Study.	Case series.	488 tumours entered onto a clinical trial evaluated for quality control purposes. Of these, 418 were clinically and pathologically evaluable, including 335 cases of STS, 58 mesotheliomas, 9 osteosarcomas and 16 chondrosarcomas. Comparison was between the initial diagnosis and a pathology review panel. USA	Agreement on histologic type and grade.	10%	16%	-		
Tetu *et al.* (1984)	To determine variation in the histopathologic diagnosis of soft tissue tumours.	Retrospective case series.	260 cases of soft tissue tumours referred to the Canadian Tumour Reference Centre, collected from 98 hospitals, 1981–1983. Comparison of referring diagnosis and specialised panel of pathologists. CANADA	Agreement in diagnosis of benign vs. malignant tumour, histologic subtype.	-	35%	-	Low level of agreement within specialist panel. Cases date from 1981–1983, outdated techniques and diagnostic criteria?	3-
Randall *et al.* (2004)	To determine the accuracy of histologic diagnosis of STS at not tertiary centres and the adequacy of surgical resection at these centres.	Case series.	104 patients with STS referred to a tertiary centre over a 6 year period, following treatment elsewhere. 70 patients underwent a second resection and are discussed in more detail. USA	Accuracy of histologic diagnosis and completeness of surgical resection by non-tertiary centre.	3%	32%	25%	Authors' conclusions: The incidence of errors in diagnosis and inadequate tumour resection suggest that biopsy and histologic analysis of sarcomas should be carried out by physicians experienced in their management.	3-

					Diagnosis changed on review				
Study	***Aims***	***Design***	***Population***	***Outcomes***	***To non sarcoma***	***Sarcoma subtype***	***Grade***	***Comments***	***Level***
Remagen (1992)	To review the diagnostic accuracy of cases referred to the Swiss Society of Pathology Bone Tumour Registry.	Case series.	4500 bone tumours excluding the skull. 1500 cases were referred from the Basel region and 3000 referred from elsewhere (including other countries). SWITZERLAND	Diagnostic agreement.	5%	19%	-	German language paper, results extracted from English abstract only. Author's conclusions: It is important that close collaboration is established between clinician, radiologist and pathologist to produce the correct diagnosis and deliver appropriate treatment.	3-
(van Dalen 2000)	To review retroperitoneal STS diagnoses recorded in the Dutch National Database of Pathology 1989-1994.	Case series.	Population based case series of 143 patients with retroperitoneal STS diagnosed between 1989 and 1994. Series included: 54 liposarcoma, 42 leiomyosarcoma and 10 MFH. NETHERLANDS	Agreement for sarcoma subtype and grade between original report and review panel.	4%	24%	36%	No reason given why the review panel should be considered more accurate than the original diagnosis.	3-
Grimer *et al.* (2001)	To review the histopathological diagnoses of all cases of musculoskeletal tumours diagnosed in a single specialist unit.	Retrospective case series.	1996 cases of musculoskeletal tumours 1985–1993. Comparison was between non-expert and recognized expert musculoskeletal pathologists. UK	Agreement on general diagnosis and grade of tumour.	Major errors occurred in 87/1996 (4%) of cases. Under-diagnosis of malignancy occurred in 21/1996 (1%) of cases. Over-diagnosis of malignancy occurred in 36/1996 (2%) of cases. In 54/1996 cases (3%) errors resulted in a significant change in the active management of the patients. Authors' conclusions: The MDT review of all musculoskeletal tumour diagnoses is mandatory before treatment is commenced. No MDT member should ever work in isolation. The regular audit of all aspects of a musculoskeletal tumour unit is mandatory.			All cases were reviewed, representing a broad spectrum of disease. Expert pathologist was not blind to original diagnosis.	3++

Study	Aims	Design	Population	Outcomes	Diagnosis changed on review: To non sarcoma	Diagnosis changed on review: Sarcoma subtype	Diagnosis changed on review: Grade	Comments	Level
Mankin *et al.* (1996)	To determine the frequency of errors, complications, alterations in outcome of biopsies of primary malignant musculoskeletal sarcomas. (FOLLOW UP TO PREVIOUS SIMILAR STUDY, 1982)	Retrospective case series.	25 surgeons from 21 institutions submitted cases of 597 patients. 235 cases (39%) were STS and 362 (61%) bone sarcomas. Comparison was made between diagnosis on the basis of the biopsy and the definitive diagnosis. USA	Errors in diagnosis (diagnosis on the basis of the biopsy vs. definitive diagnosis).	Error in diagnosis (musculoskeletal treatment centres vs. referring institutions): 39/316 vs. 77/282 (13.3% vs. 27.4%, RR: 0.45). Authors' conclusions: Authors make recommendations about ensuring adequacy of representative tissue on biopsy; interpretation by a suitably experienced pathologist; referral to a treatment centre if local arrangements are not adequate.			Treatment centre biopsies were defined as those performed by orthopaedic oncologist members of the Musculoskeletal Tumour Society. Unclear what proportion of surgeons responded to the questionnaire.	3+
Stiller *et al.* (2000)	To calculate population based survival rates for osteosarcoma and Ewing's sarcoma among patients younger than 40 years, and to identify prognostic factors related to patterns of care.	Retrospective cohort study.	2843 people with primary malignant bone tumours diagnosed at age 0-39 years in the UK, 1980–1994. Patients were identified through the NCRT, English regional cancer registries and Scottish and Welsh national cancer registries. The UKCCSG and specialist bone tumour registries were also checked. Lists of patients entered in osteosarcoma and Ewing's sarcoma trials were supplied by the MRC cancer trials office and the UKCCSG. UK	Diagnostic agreement.	Diagnoses provided by the specialist bone tumour registers and from clinical trials were based on central pathology review, as were those from the northern region young persons' malignant disease registry. 1317/2843 (46%) of patients had such a review diagnosis. These review diagnoses were compared to those entered into the English regional and national Scottish or Welsh cancer registries. Diagnoses concurred in 88% of cases. The error rate was therefore 12% at most. Authors suggest that some of the inaccuracy could be due to failure to update the cancer registry when new information became available. The most common sort of difference was the cancer registry having a less specific diagnosis than the review source.			Only a subset of the results is presented in this appraisal, see other evidence tables.	2+

Study	Aims	Design	Population	Outcomes	Diagnosis changed on review: To non sarcoma / Sarcoma subtype / Grade	Comments	Level
Barlow & Newman (1994)	To review the contents of the Leeds Regional Bone Tumour Registry with regard to the shoulder.	Within group comparison.	145 primary bone tumours of the shoulder region in a registry of 2039 cases gathered from 1958–1994. 73 cases were malignant and 72 benign. UK	Tumour site and type, diagnostic accuracy.	Tumour site: Seventy-five per cent of tumours occurred in the proximal humerus, 20% in the scapula and 5% in the outer half of the clavicle. Tumour type: 73 cases were malignant and 72 benign. Commonest tumour types were: unicameral cyst 40 cases, osteosarcoma 26 cases and chondrosarcoma 21 cases. Simple bone cyst was the commonest diagnosis in children, chondrosarcoma in the middle age group and osteosarcoma in the over 60s. Diagnostic accuracy: Cases submitted to the register were subject to central diagnostic review. In 13 cases the preoperative diagnosis was deemed incorrect and resulted in suboptimal management. A biopsy was performed before surgery in 82/145 (57%) cases. In the remaining 63/145 (43%) patient's treatment was undertaken on the basis of clinical findings alone. In 11/145 (8%) of cases the histological diagnosis of the tumour registry differed from the referring pathologist's diagnosis with important clinical implications. In 6/145 (4%) patient's diagnosis was delayed by failure to order a radiological examination. In 7/145 (5%) patient's diagnosis was delayed by failure to take an adequate biopsy. Authors' conclusions: An adequate biopsy specimen obtained at the time of presentation should be referred to a specialist pathologist or tumour panel for optimal management. Increased awareness of the causes of local symptoms, prompt radiological	Some cases could date back to 1958, raising questions of diagnostic techniques and criteria.	3+

Study	Aims	Design	Population	Outcomes	Diagnosis changed on review: To non sarcoma	Diagnosis changed on review: Sarcoma subtype	Diagnosis changed on review: Grade	Comments	Level
					investigation and expeditious biopsy of suspicious lesions are basic prerequisites for the satisfactory management of these patients.				

Table 3.b What is the clinical utility of cytogenetic testing and molecular pathology in people with sarcoma?

Abbreviations: CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; ESFT, Ewing's sarcoma family of tumours; FISH, fluorescence in situ hybridisation; GIST, gastrointestinal stromal tumour; HR, hazard ratio; KIT, proto-oncogenic receptor tyrosine kinase; MLS, myxoid liposarcoma; NCI, National Cancer Institute; NOS, not otherwise specified; PDGFRA, platelet derived growth factor receptor α; RR, relative risk; RT-PCR, reverse transcriptase polymerase chain reaction; SSG, Scandinavian sarcoma group; STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Antonescu *et al.* (2001)	To determine the impact of TLS-CHOP fusion gene structure and p53 status on clinical outcome in patients with myxoid liposarcoma (MLS).	Retrospective case series.	82 cases of mixoidliposarcoma previously confirmed to harbour a CHOP rearrangement. Cases originated from 3 institutions. USA	TLS-CHOP fusion type. Time to local recurrence, to distant metastasis and to death from disease.	Most MLS were >10 cm (73%), arising in the thigh (70%), and localized at presentation (89%). The round-cell component was <5% in 47 (57%) cases and ≥ =5% in 35 (43%). The TLS-CHOP fusion transcript was type 5-2 in 55 (67%), type 7-2 in 16 cases (20%), and type 8-2 in 8 (10%). One tumour had a unique variant fusion, between exon 6 TLS and exon 2 CHOP. Two other cases (2%) showed an EWS-CHOP fusion transcript. High histological grade (defined as ≥ =5% round-cell; $p < 0.01$), presence of necrosis (> or =5% of tumour mass; $p < 0.05$), and over expression of P53 ($p < 0.001$) correlated with reduced metastatic disease-free survival in localized tumours. The presence of negative surgical margins ($p < 0.01$) and extremity location ($p = 0.02$) were found to be significant in predicting local recurrence in the entire group as well as localized cases by univariate and multivariate analysis. There was no significant correlation between TLS-CHOP transcript type and histological grade or disease-specific survival.	Prognostic parameters analyzed included age, location, size, percentage of round cell (RC) component, areas of increased cellularity, necrosis, and surgical margins. Detection of TLS-CHOP (or EWS-CHOP) fusion transcripts can serve as a diagnostic adjunct in cases of MLS, but does not appear to predict clinical outcome.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Antonescu *et al.* (2003)	To investigate the prognostic significance of KIT exon 9, 11, 13 and 17 mutations in patients with GIST.	Retrospective case series.	Patients who were diagnosed with KIT positive primary or recurrent GIST between 1982 and 2002. Original pathology was reviewed for the study. 120 cases met the inclusion criteria. 5% of patients had liver metastases at presentation. USA	Overall survival. Disease free survival, reported as local recurrence free survival and liver metastasis free survival. Median follow up was 34 months.	KIT mutations were detected in 94/120 (78%) patients. 81/120 (67%) of patients had mutations in exon 11 and 13/120 (11%) in exon 9. No exon 13 or 17 mutations were detected. Overall survival: Adverse prognostic factors were: large tumour size (=10cm), presence of intra-abdominal spread at diagnosis and high mitotic activity. Local recurrence free survival: Adverse prognostic factors were: large tumour size (=10cm), presence of intraabdominal spread at diagnosis and high mitotic activity. Distant metastasis free survival: Adverse prognostic factor was: high mitotic activity. The 10 patients with exon 9 mutations, with a year's follow up data, all developed intra-abdominal disease and/or distant metastases. Authors' conclusions: Most KIT-positive GISTs show KIT mutations in exon 11, in one of 2 hot spots. KIT exon 9 mutations seem to define a subset of GISTs located predominantly in the small bowel with unfavourable clinical course.	The treatment received by the patients is not reported or included in the analysis. Mutation type was not included as a prognostic factor. Age, sex, tumour size, location, disease stage, mitotic index and morphological type were considered as prognostic factors. The technique used to evaluate prognostic factors is not reported.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Borden *et al.* (2003)	Summary and recommendations for sarcoma molecular pathology, management and targeted therapy. From the NCI sarcoma state of the science meeting, Bethesda, MD, USA, 17/6/2002	Consensus statement.			Notes that genetics of sarcomas can be broadly divided into 2 types: those with specific genetic alterations and usually simple karyotypes and those with non-specific genetic alterations and complex, unbalanced karyotypes. Of the sarcomas with specific genetic alterations, many involve chromosomal translocations with resulting fusion genes. Most of these fusion genes have been identified and are potentially useful diagnostic markers for sarcoma types. These include 11 different gene fusions involving the EWS gene or EWS family members found in 5 different sarcomas, and 10 other types of fusions found in 7 other sarcomas. Recommendations are made regarding the procurement of tissue for pathology, the standardization of pathology reporting and the need for molecular pathology resources.		4
de Alava *et al.* (1998)	To investigate the clinical significance of molecular heterogeneity of EWS-FLI fusion transcripts in Ewing sarcoma.	Case series.	112 patients with Ewing sarcoma in which EWS-FLI1 fusion transcripts were identified using RT-PCR. Patients were selected by review of molecular pathology data from 5 institutions. USA CANADA SPAIN	Overall survival.	Adequate treatment and follow up data were available in 99/112 patients treated with curative intent. Median follow up in these 99 patients was 26 months (range, 1 to 140 months). Among the 99 patients suitable for survival analysis, the tumours in 64 patients contained the type 1 fusion and in 35 patients contained less common fusion types. Stage at presentation was localized in 74 patients and metastatic in 25. Metastases (relative risk [RR] = 2.6; P =.008), and type 1 EWS-FLI1 fusion (RR = 0.37; P =.014) were, respectively, independent negative and positive prognostic factors for overall survival by multivariate analysis. Among 74 patients with localized tumours, the type 1 EWS-FLI1 fusion was also a significant positive predictor of overall survival (RR = 0.32; P =.034) by multivariate analysis.		3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Debiec-Rychter *et al.* (2004)	To investigate whether the mutational status of a GIST predicts response to imatinib.	Retrospective case series.	37 patients with GIST who were enrolled in 2 EORTC clinical trials of imatinib. 3 institutions contributed tissue blocks. All patients had histologically confirmed metastatic or unresectable GIST. All patients had tumours that expressed the CD117 antigen. BELGIUM, NETHERLANDS, UK	Response to imatinib therapy, overall survival and event free survival.	Patients enrolled in the phase I EORTC trial received imatinib in doses of 400mg daily, 300mg twice daily, 400mg twice daily or 500mg twice daily. Those in the phase II trial received 400mg twice daily. Tissue blocks from 37 patients were tested for c-KIT mutations and in 33 cases for PDGFRA mutations. Response to imatinib therapy: 21/29 (72%) patients with KIT mutations showed a partial response to therapy and 7/29 (24%) had stable disease. Patients with exon 11 mutations were more likely to achieve partial response (20/24; 83%) than other patients (3/13; 23%). The responses of other mutation types were not analysed statistically as there were too few cases, although all 4 patients with exon 9 mutations showed either partial response or stable disease. Overall and event free survival: For the whole group, overall 106 week survival was 78%. On univariate analysis patients with detectable c-kit mutations had better survival than patients whose GIST did not have a detectable c-kit mutation (p=0.015). The progression free survival of the group was 47% at 106 weeks. Patients whose GIST had a detectable c-kit mutation were less likely to experience disease progression than other patients (p=0.03). Median progression free survival in patients with exon 11 KIT mutations was 849 days compared to 327 days in the other patients. Authors' conclusions: The mutational status of the c-KIT/PDGFRA oncoproteins could be useful to predict the clinical response of patients to imatinib therapy.	Of 67 patients enrolled in the trials, tissue blocks were only available from 37, possible selection bias. The starting point was used to measure survival is unclear. Other prognostic factors (tumour size, mitotic count and cytomorphology) were not included in the survival analysis.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Heinrich *et al.* (2003)	To examine the relationship between mutations in KIT or PDGFRA and clinical response to imatinib in patients with GIST.	Retrospective case series.	127 patients with GIST who were enrolled in a multi-centre phase II clinical trial of imatinib. Patient characteristics are published, along with the primary clinical trial results, elsewhere.	Response to imatinib therapy, event free survival and overall survival.	112/127 (86%) of patients had KIT mutations. The 15 tumours without a KIT mutation were tested for PDGFRA mutations and 6 were detected. Response to imatinib: No patients experienced a complete response to therapy. Patients with exon 11 KIT mutations were more likely to have a partial response to imatinib therapy than those with an exon 9 KIT mutation or no detectable KIT mutation. The impact of PDGFRA mutation could not be assessed due to the limited number of cases. A stepwise logistic regression showed the presence of a KIT exon 11 mutation to be the strongest predictor of response to therapy (hazard ratio, 0.27; 95% CI, 0.08 to 0.92). Event-free and overall survival: Cox proportional hazards models were used (in a stepwise fashion) to select prognostic factors for overall and disease free survival. Significant adverse prognostic factors for event-free survival (at the $p<0.05$ level) were: poor performance status at baseline, daily dose less than 600mg and lack of KIT exon 11 mutation. Significant adverse prognostic factors for overall survival (at the $p<0.05$ level) were: poor performance status at baseline, daily dose less than 600mg and lack of KIT exon 11 mutation. Patients with a KIT exon 9 mutation had better overall survival than those with no detected mutation or a PDGFRA mutation. Authors' conclusions: Activating mutations of KIT or PDGFRA are found in the majority of GISTs and the mutational status of these oncoproteins is predictive of clinical response to imatinib. PDGFRA mutations can explain response and sensitivity to imatinib in patients with GISTs lacking KIT mutations.		3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Hogendoorn *et al.* (2004a)		Consensus statement.			Discusses the WHO classification of STS tumours and the important role of immunophenotyping and molecular genetics in classification. Authors argue that accurate histological subtyping of STS is necessary for clinical trials, since future treatments may be targeted at subtypes. To this end, the authors state: "The collection of fresh-frozen tissue should become routine for every STS (both from diagnostic biopsies and resection specimens) across all centres".		4
Kawai *et al.* (1998)	To determine the influence of the two alternative forms of the SYT-SSX fusion gene on tumour morphology and clinical outcome in patients with synovial sarcoma.	Case series.	45 patients with histologically verified synovial sarcoma (33 monophasic and 12 biphasic). SYT-SSX fusion transcripts were analyzed using RT-PCR. Patients were all treated at the same institution between 1982 and 1997. USA	5 year disease-free survival and overall survival.	Of the 45 synovial sarcomas 29 (64%) had a SYT-SSX1 fusion transcript and 16 (36%) a SYT-SSX2 fusion transcript. All 12 biphasic synovial sarcomas had a SYT-SSX1 fusion transcript, and all 16 tumours that were positive for SYT-SSX2 were monophasic. Post-operative follow up ranged from 2 to 180 months (mean 40, median 26). The only significant factor related to survival was presence of metastases at diagnosis (p=0.001 by multivariate analysis). In the 39 patients with localized tumours at diagnosis, survival analysis showed that the 15 patients with SYT-SSX2 had significantly better metastasis-free survival than the 24 patients with SYT-SSX1 (P=0.03 by multivariate analysis; relative risk, 3.0). There were no significant correlations between the type of SYT-SSX transcript and age, sex, tumour location and size, whether there were metastases at diagnosis, or whether patients underwent chemotherapy. Histologic subtype alone was not prognostically important. Authors' conclusions: The type of SYT-SSX fusion transcript correlates	Histopathology was reviewed blind to the molecular genetic data.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					with both the histologic subtype and the clinical behaviour of synovial sarcoma. SYT-SSX fusion transcripts are a defining diagnostic marker of synovial sarcomas and may also yield important independent prognostic information.		
Kelly *et al.* (1997)	To evaluate the clinical features of the common PAX3-FKHR and variant PAX7-FKHR gene fusions observed in rhabdomyosarcoma.	Case series.	34 patients with rhabdomyosarcoma containing the PAX3-FKHR (n=18) or PAX7-FKHR (n=16) gene fusion, identified using RT-PCR. In the PAX3 group histology was reported as alveolar (n=15), embryonal (n=1), mixed embryonal and alveolar (n=1) and NOS (n=1). In the PAX7 group histology was reported as alveolar (n=10), embryonal (n=2), mixed embryonal and alveolar (n=1) and NOS (n=3). Patients were selected by review of molecular pathology data from 4 institutions. USA CANADA	Disease free and overall survival	The median follow up duration was 29 months (range 9–61) and 24 months (range 11–60) for the PAX3 and PAX7 groups respectively. The group with a PAX7-FKHR fusion was younger (P =.01) and presented more often with an extremity lesion (82% v 22%; P =.001). PAX7-FKHR tumours were more often localized than PAX3-FKHR tumours (P =.03). In patients with metastatic disease at diagnosis, the patterns were different: PAX7-FKHR patients had metastatic disease that involved only bone (n = 2) and distant nodes (n = 2), while the PAX3-FKHR group had multiple sites involved, including bone (n = 7), marrow (n = 7), lungs (n = 3), distant nodes (n = 2), skin (n = 1), and brain (n = 1). No significant difference in relapse rate was observed. 4 year event-free survival for the PAX7-FKHR group was significantly longer than for the PAX7-FKHR group (43% vs. 17%, P =.04). Authors' conclusions: The results suggest that the common PAX3-FKHR and the variant PAX7-FKHR fusions are associated with distinct clinical phenotypes. Identification of fusion gene status may be a useful diagnostic tool in rhabdomyosarcoma.	There was no central pathologic review. Adjustment was not made for other prognostic factors, such as tumour size, site and depth; patient age and surgical margins, in the survival analysis. The importance of PAX3 / PAX7 gene fusion as an independent prognostic factor is therefore difficult to estimate.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Kim *et al.* (2004)	To examine the prognostic significance of KIT mutations in patients with GIST.	Retrospective case series.	86 patients with KIT positive GIST. Patients were included if they had localised disease at presentation and had received curative surgery. Patients were treated between 1990 and 2001 in a single institution. KOREA	Disease free survival.	64/86 (74%) patients had detectable KIT mutations. Of these 61 (71%) were in exon 11 and 3 (3%) were in exon 9. No exon 13 or 17 mutations were demonstrated. The presence of a KIT mutation was associated with high mitotic count and dense cellularity. In a multivariate analysis, presence of a KIT mutation, high mitotic count and tumour size = 5cm were independent adverse prognostic factors for disease free survival.		3+
Ladanyi *et al.* (2002)	To examine, in synovial sarcoma, whether patients with SYT-SSX2 tumours do better than those with SYT-SSX1 tumours.	Case series and prognosis study.	243 patients (age range, 6–82) with synovial sarcoma. SYT-SSX1 and SYT-SSX2 fusions were detected in 147 tumours (61%) and 91 tumours (37%), respectively. Histologically, 61 (25%) were classified as biphasic type and 180 (74%) as monophasic type based on the presence or absence of areas of glandular epithelial differentiation, respectively. Study was multi-institutional with 7 centres contributing. USA, SWEDEN, UK	Overall survival.	Median follow up was 2.7 years (range 0.05 to 25.5 years). Median and 5-year overall survivals for the SYT-SSX1 and SYT-SSX2 groups were 6.1 years and 53%, and 13.7 years and 73%, respectively. Univariate tests (log-rank tests): Overall survival was significantly better among SYT-SSX2 cases (P = 0.03), among cases localized at diagnosis (P < 0.0001), and among patients with primary tumours < 5 cm in greatest dimension (P = 0.01). Age, sex, histological type, and axial versus peripheral primary site had no impact on overall survival. The impact of fusion type on survival remained significant when stratified for primary tumour size (P = 0.03) but was no longer significant when stratified for disease status at presentation. This may reflect the tendency for patients with SYT-SSX1 tumours to present more often with metastatic disease (P = 0.05). Multivariate tests (Cox regression): In all patients: Cox regression identified disease status (P < 0.0001) and primary tumour size (P = 0.04) as the only factors independently predictive of overall survival in the subset of 160 patients with information on all of the factors.	Included the Kawai et al. (1998) and Nilsson et al (1999) cohorts. Follow up data missing for 10/243 patients. There was variability in the method used for SYT-SSX fusion type analysis. Some groups used RT-PCR others used FISH.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					In patients with localized disease at diagnosis: There was a strong association of fusion type and morphology (P < 0.001), with almost all of the SYT-SSX2 tumours showing absence of glandular differentiation (monophasic histology) and almost all of the biphasic tumours containing SYT-SSX1. Authors' conclusions: Overall, SYT-SSX fusion type appears to be the single most significant prognostic factor by multivariate analysis in patients with localized disease at diagnosis. SYT-SSX fusion type also appears to exert part of its impact on prognosis before presentation through its association with stage at diagnosis.		
Nilsson *et al.* (1999)	To examine the relative prognoses of the SYT-SSX1 and SYT-SSX2 variants of synovial sarcoma.	Case series.	33 patients with histologically verified primary synovial sarcoma. Patients were referred to a single SSG centre between 1988 and 1998. SWEDEN	Metastasis free survival and overall survival.	All patients were treated surgically with curative intent. Mean follow up was 46 months, range 2–111 months. RT-PCR was used to assess the type of fusion transcript in each case. The proliferation rate was analyzed using anti-Ki-67 antibodies. One case carrying an atypical transcript was excluded, leaving 13 SYT-SSX1 and 19 SYT-SSX2 cases for analysis. The hazard ratio (with respect to metastasis-free survival for patients with SYT-SSX1 versus patients with SYT-SSX2 fusion transcripts was 7.4 (95% confidence interval, 1.5-36; log-rank P = 0.004). There was also an association with reduced overall survival for patients with SYT-SSX1 compared to patients with SYT-SSX2 (hazard ratio, 8.5; 95% confidence interval, 1.0–73; log-rank P = 0.02). The 5-year metastasis-free survival for patients with SYT-SSX1 was 42% versus 89% for patients with SYT-SSX2. There was a significant association between SYT-SSX1 and a high tumour proliferation rate (P = 0.02).	Small but otherwise well conducted study. The type of SYT-SSX fusion transcript appears to be a predictor of clinical outcome in patients with synovial sarcoma.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Riley *et al.* (2003)	To identify measures of potential clinical value for the areas of screening, diagnosis, prognosis and monitoring in ESFT and neuroblastoma	Systematic review and meta analysis.	Eighty-four 'relevant' papers were identified which studied 70 different markers in ESFT. Eighty-four papers related to diagnosis, 45 to prognosis and five to monitoring, but none to screening. Also 428 studies of markers in neuroblastoma were identified (not considered in this appraisal).	Overall survival, disease free survival and metastasis free survival. Meta-analyses were conducted using hazard ratios of marker to non-marker groups.	Meta-analysis of the data from the diagnosis or monitoring papers was not possible because of the poor quality and reporting of data. Meta-analysis of prognostic papers was possible but authors emphasise the results must be treated with caution given problems with poor reporting in many of the studies. Expression of the EWS–FLI type 1 fusion transcript in tumours from patients with localised disease was associated with a more favourable outcome and reduced risk of disease recurrence or death, compared with expression of other EWS–ETS fusion transcripts (HR=0.171, 95% CI = 0.079 to 0.373, p not reported). High levels of serum lactate dehydrogenase and lack of S-100 protein expression in the tumour were also found to be useful prognostic indicators. Authors' conclusion: For ESFT the following were found to be potentially important prognostic markers associated with poorer outcome: lack of expression of the EWS-FLI type 1 fusion transcript in the tumour, high levels of serum lactate dehydrogenase and lack of S-100 protein expression in the tumour.		2++
Singer *et al.* (2002)	To evaluate the prognostic significance of KIT mutations in patients with GIST.	Retrospective case series.	48 patients with localised KIT positive GIST who underwent surgical resection at one institution between 1990 and 2000. 4 patients had regional peritoneal spread at presentation, none had distant metastases. USA	Disease free survival.	44/48 (92%) of patients had demonstrable KIT mutations. These consisted of 34 (71%) exon 11 mutations, 6 (13%) exon 9 mutations, and 2 (4%) cases each of mutations in exon 13 and 17. The overall five year disease free survival was 41%±6%. Significant adverse prognostic factors for disease free survival, on univariate analysis, were tumour size >10cm, high mitotic count, and mixed spindle and epithelioid cytomorphology. Patients with missense exon 11 mutations had better disease free survival than patient with other mutations.	Low numbers of patients prevented full analysis of survival by mutation type. 13 patients received chemotherapy, but regimen is not reported. Median follow up is not reported.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					On multivariate analysis the following independent adverse prognostic factors were identified: high mitotic count, mixed cytomorphology, presence of a deletion or insertion exon 11 mutation, and male sex. Authors' conclusions: Mitotic activity and histologic subtype were the most important prognostic factors in this series. These results suggest that KIT mutation and activation are important in GIST pathogenesis and may provide prognostic information.		

Multidisciplinary sarcoma teams and centralisation of treatment

The questions

a) Should all people with sarcoma be reviewed by a specialist MDT?

b) Does hospital case volume have an effect on outcomes for patients with sarcoma?

c) Is there any evidence that a 'hub and spoke' structure for delivery of care affects patient outcome?

Nature of the evidence

a) Should all people with sarcoma be reviewed by a specialist MDT?

Soft Tissue Sarcoma

Five observational studies used cancer registries and/or hospital records to compare the outcomes of patients reviewed by a sarcoma MDT with those not reviewed by such an MDT. Four studies, two from Scandinavia (Bauer *et al.* 2001; Wiklund *et al.* 1996) and one each from Canada (Paszat *et al.* 2002) and the UK (Bhangu *et al.* 2004) included only people with STS of the limb, limb girdle or trunk. A French audit (Ray-Coquard *et al.* 2004) contained a majority of patients with extremity or truncal STS but also some patients with STS at other anatomical sites. The UK study was the only one to adjust for differences in case mix in its analyses.

The outcomes reported were: overall survival (Bhangu *et al.* 2004; Paszat *et al.* 2002; Wiklund *et al.* 1996), disease free survival (Bauer *et al.* 2001; Bhangu *et al.* 2004; Ray-Coquard *et al.* 2004; Wiklund *et al.* 1996), risk of amputation (Paszat *et al.* 2002) and the adequacy of surgical margins (Bauer *et al.* 2001; Bhangu *et al.* 2004; Ray-Coquard *et al.* 2004).

Studies used the following groups for comparison with patients reviewed by MDT: patients treated in district general hospitals without a sarcoma MDT (Bhangu *et al.* 2004; Wiklund *et al.* 1996; Bauer *et al.* 2001) patients not formally reviewed by

a sarcoma MDT (Ray-Coquard *et al.* 2004), historical data from an institution prior to introduction of an MDT (Wiklund *et al.* 1996) and patients who did not attend an multidisciplinary cancer centre within 3 months of diagnosis (Paszat *et al.* 2002).

Bone sarcomas

Evidence about MDT management for people with bone sarcomas was limited to a UK study (Stiller *et al.* 2000) of patterns of care and survival in people younger than 40 years with bone sarcoma. This study partially adjusted for case mix in an analysis of overall survival. The study design allowed a comparison of outcomes in patients managed by a specialist MDT at the two supraregional NSCAG bone tumour services or 20 UKCCSG paediatric oncology centres with those treated at other hospitals, where management by a bone sarcoma MDT was unlikely.

b) Does hospital case volume have an effect on outcomes for patients with sarcoma?

Evidence about hospital case volume and outcome in people with sarcoma was limited to two population based observational studies (Paszat *et al.* 2002; van Dalen 2000) and a cohort study (Stiller *et al.* 2000). An observational study (Nijhuis *et al.* 2001) examined hospital case volume and compliance with clinical guidelines for patients with sarcoma.

The UK bone tumour cohort study (Stiller *et al.* 2000) examined the effect of hospital case volume on the survival of people with osteosarcoma or Ewing's sarcoma. Hospitals were categorised according to the average number of new patients treated per year: 0–1, 2–4, 5–9 and more than 9 patients. Partial adjustment for case mix was made in the analysis.

A large population based Canadian observational study (Paszat *et al.* 2002) of people with extremity STS compared patient survival and risk of amputation in three categories of hospital case volume: less than 2, between 2 and 5 and more than 5 patients per year on average. The study adjusted for case mix in its analysis.

A population based observational study (van Dalen 2000) in the Netherlands compared the outcomes of people with retroperitoneal STS in hospitals treating an average of less than one patient per year with those in hospitals treating more than one patient per year. Adjustment was made for case mix.

Another Netherlands study used cancer registry data to examine the relationship between case volume in district hospitals and conformity to diagnostic guidelines for STS (Nijhuis *et al.* 2001). There were two case volume categories: less than two patients per year on average or more than 2 patients per year.

c) Is there any evidence that a 'hub and spoke' structure for delivery of care affects outcome for patients with cancer?

No evidence from studies of people with sarcoma was found. Due to the scarcity of research in this area the scope of the question was widened to include any evaluation of hub and spoke healthcare delivery models. A systematic review and modelling study of high quality compared patient outcomes in 'hub and spoke', centralised and localised service delivery models for vascular services (Michaels *et al.* 2000). One systematic review of good quality examined accessibility and patient outcomes in cancer services (Ferguson 1996).

Evidence on peoples' views about travelling for treatment is reviewed in the patient perspectives section.

Summary of the supporting evidence for the recommendations

a) Should all patients with sarcoma be reviewed by a specialist MDT?

MDTs for soft tissue sarcomas

There is consistent evidence from observational studies that outcomes are better in patients managed by an STS MDT, but it is unclear to what extent MDT management is responsible for this difference. Multidisciplinary sarcoma teams tend to be located in specialist centres which in turn treat the greatest numbers of people, and it is difficult to estimate the contribution of the MDT service model to better patient outcomes. Pre-treatment differences between patients cared for by specialist and non-specialist centres could confound comparisons between the

two settings, but only two studies (Paszat *et al.* 2002; Bhangu *et al.* 2004) adjusted for case mix.

There was evidence of an overall survival advantage for those people with STS reviewed by a sarcoma MDT, in the three studies that reported this outcome (Bhangu *et al.* 2004; Paszat *et al.* 2002; Wiklund *et al.* 1996). The four studies that considered disease-free survival (Bauer *et al.* 2001; Bhangu *et al.* 2004; Ray-Coquard *et al.* 2004; Wiklund *et al.* 1996) found an advantage for those patients who were treated by a sarcoma MDT.

None of the three comparisons of surgical resection margins were case mix adjusted (Bauer *et al.* 2001; Bhangu *et al.* 2004; Ray-Coquard *et al.* 2004). Two studies reported that wide or compartmental surgical resections were more likely for patients treated by a sarcoma MDT. The UK study (Bhangu *et al.* 2004) did not observe a difference between the rate of wide or compartmental resections achieved by the sarcoma MDT and by district general hospitals in the same region, although 45% of the patients treated by the MDT had large, high-grade, deep sarcomas, compared to 21% of those treated at district general hospitals.

Canadian patients who did not attend a multidisciplinary cancer centre within 3 months of diagnosis were at increased risk of amputation (Paszat *et al.* 2002).

Other differences between patterns of care provided by specialist sarcoma multidisciplinary teams and other treatment centres included better conformity to clinical practice guidelines by multidisciplinary teams and greater use of preoperative imaging and biopsy.

MDTs for bone sarcomas

In the Stiller and co-workers study (Stiller *et al.* 2000) patients managed by a specialist MDT at the two supraregional bone tumour services or 20 UKCCSG paediatric oncology centres had improved overall survival when compared to those treated at other hospitals. This study was not designed to address the issue of MDT management, however, and it is unknown whether any of the other hospitals had MDTs treating bone sarcomas.

b) Does hospital case volume have an effect on outcomes for patients with sarcoma?

There was insufficient evidence to draw conclusions about the impact of hospital case volume on outcomes of people with sarcoma. The few studies identified were unlikely to answer the question; due to the rarity of sarcoma there are few truly high case volume hospitals or surgeons, so most studies made comparisons between low volume centres. In the absence of evidence to indicate the appropriate case load for a sarcoma unit or surgeon, definitions of 'high case volume' were not defined *a priori* but derived from study results, ranging from one patient per year to ten or more patients per year. Evidence from studies of other cancers suggests there is a positive relationship between case volume and patient outcome for complex or high-risk surgery (NICE *Improving Outcomes in Colorectal Cancer*).

In the study of Pazat and co-workers (Paszat *et al.* 2002), the case volume of the hospital providing definitive treatment was not statistically associated with risk of amputation or overall survival. A beneficial effect of hospital case volume on survival was observed for people with Ewing's sarcoma but not for those with osteosarcoma, in the UK study of Stiller and co-workers (Stiller *et al.* 2000).

In van Dalen's study of retroperitoneal STS (van Dalen 2000) patients treated in higher volume hospitals were more likely to receive complete resection of their tumour, but no effect on survival was observed. This is probably due to better preoperative assessment and selection of candidates for surgery in the higher volume hospitals.

The second Netherlands study (Nijhuis *et al.* 2001) reported better adherence to guidelines for the diagnosis of soft tissue tumours greater than 3cm in district hospitals treating more than two patients per year.

In four of the studies reporting improved outcomes for people with limb or truncal STS treated in specialist centres when compared with non-specialist settings (see table 7.a) it was possible to calculate the mean number of new patients per year treated in the specialist centre. Patients per year ranged from 20 to 32 (although true case volume was likely to be greater since patients with sarcomas at other

anatomical sites were excluded). No studies comparing the outcomes in different specialist centres by case volume were identified.

c) Is there any evidence that a 'hub and spoke' structure for delivery of care affects outcome for patients with cancer?

In a study comparing centralised, hub and spoke, and localised vascular services models (Michaels *et al.* 2000), both centralised and hub and spoke models were associated with improved patient outcomes when compared to the localised model.

The argument that specialisation and case volume are associated with improved outcomes supports the hub and spoke model (see evidence tables 2.a, 4.a, 5.a, 6.a and 7.a) although such arguments also favour the fully centralised service model. Reduction of the patient's burden of travel (see evidence table 1.a) is a major advantage of the hub and spoke model over a fully centralised service.

In the second systematic review (Ferguson 1996), direct evidence of the relationship between travelling distance and mortality or morbidity was scarce, although two studies of people with cancer indicated that outcomes are not adversely affected by travelling distance. There was some evidence that use of diagnostic services may be more sensitive to distance effects than use of treatment services; people being more willing to travel for treatment services than for diagnostic services.

Table 4.a Should all patients with sarcoma be reviewed by a specialist MDT?

Abbreviations: CI, confidence interval; CNS, central nervous system; CT, computed tomography; DFP, dermatofibrosarcoma protuberans; DGH, district general hospital; HR, hazard ratio; KS, Kaposi sarcoma; MDT, multidisciplinary team; MRC, Medical Research Council; MRI, magnetic resonance imaging; NRCT, National Register of Childhood Tumours; RHA, regional health authority; RR, relative risk; SSG, Scandinavian Sarcoma Group; STS, soft tissue sarcoma; UKCCSG, United Kingdom Children's Cancer Study Group.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Bhangu *et al.* (2004)	To investigate whether there is evidence that patients with STS do better if treated in a specialist centre compared with DGHs.	Retrospective case series.	263 patients diagnosed and treated with curative intent for STS 1994–96 in one RHA. Patients were treated in a specialist centre (SC) (n=96) or at 1 of 38 DGHs (n=164) Follow up min 5 years. Exclusions: KS, head and neck, retroperitoneal tumours. UK	Overall survival; local recurrence.	Specialist centre (SC) defined as 'unit with MDT managing sarcomas'. Adequate excision margins: DGH 35%, SC 39%. Univariate analysis (log-rank test) showed no significant difference between the 2 settings in local recurrence and overall survival. 5 years local recurrence rate: DGH 39%, SC 19%. Overall 5 year survival rate of non-metastatic patients: 58% in both settings. Multivariate analysis (Cox regression) showed patients treated at the SC had a small survival advantage (HR: 0.59; 95% CI: 0.35–0.99) taking into account age and tumour size, depth and grade. Authors' conclusions: Centralisation of treatment improves local control in all patients with sarcoma and survival in some.	Patients treated initially at DGHs for small lumps but subsequently referred to SC due to post-operative diagnosis analysed in SC set. Patients treated at SC tended to be younger with larger tumours with a greater proportion of both deep and high-grade tumours, than those at the DGHs. Metastatic patients excluded from analysis.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Paszat *et al.* (2002)	To describe STS of the extremities case volumes of hospitals and cancer centres (to provide a surrogate measure of specialised expertise); to describe the proportion of cases admitted to hospitals with the largest experience in treatment of STS of the extremities and the proportion of cases of STS of the extremities that attend a multidisciplinary cancer centre (as a surrogate measure of multidisciplinary care) and to describe the treatment of newly diagnosed STS of the extremities and clinical outcomes, in relation to institutional case volume.	Population-based retrospective case series.	1467 cases of extremity STS 1987–1996 in one Canadian province (Ontario). All patients aged 17 years or older. Data obtained from cancer registry, Canadian Institute for Health Information, and Radiation Oncology Research Unit database of radiation therapy records. CANADA	Overall survival; amputation; amputation or resection at any time during follow up after definitive surgery (surrogate measure of locally recurrent STS).	Using multivariate analysis the relative risk of death was 1.4 (95% CI 1.1–1.7) for patients who did not attend a multidisciplinary cancer centre within 3 months of diagnosis. The relative risk of amputation was 3.5 (95% CI 1.6–7.5) for patients who did not attend a multidisciplinary cancer centre within 3 months of diagnosis. Case volume of the hospital providing definitive treatment was not statistically associated with risk of amputation or death. Authors' conclusions: Cases not seen at a multidisciplinary cancer centre within 3 months following diagnosis of STS have an increased risk of amputation or death due to any cause.	Authors conclude that cases not seen at a multidisciplinary cancer centre within 3 months following diagnosis of STS have an increased relative risk for amputation at any time, and for death due to any cause. No clear definition of what constitutes a specialist centre. Reliability of cancer registry data? The timing of each death was not recorded (survival of 1 year and 5 years would have been coded the same). The MDT cancer centres described in this study are not surgical facilities, but provide medical and clinical oncology services.	3+
Ray-Coquard *et al.* (2004)	To assess the conformity of medical practice to clinical	Observational study – retrospective clinical audit.	100 newly diagnosed STS patients seen from 1999 to 2001. Cases were drawn at random from a series of 650	Local and distant recurrence; resection margin. Conformity of management with	7% of cases had MDT review before biopsy and there were 42% pre-surgery biopsies. Conformity to guidelines was rated 52, 81, 94 and 95% for initial surgery, radiation therapy, chemotherapy	Risk of distant recurrence for those evaluated by an MDT before surgery is not reported.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
	guidelines for the management of STS.		in a single French region. Exclusions: tumours of bone, CNS and KS; metastases at diagnosis. FRANCE	clinical practice guidelines.	and follow up respectively R0 resections were more likely (15/35 vs. 10/60, 43% vs. 17%, RR:2.53) and R2 resections less likely (7/35 vs. 36/60, 20% vs. 60%, RR:0.33) if patients had an MDT evaluation before surgery. R2 resections were less likely in University or cancer hospitals than in general hospitals (27% vs. 61%, RR:0.44, p=0.02). At multivariate analysis, pre-surgery MDT discussion, management in specialist centre and management within cancer network independently predicted conformity to guidelines. Local relapse was more likely if surgery performed by non-specialist (RR:7.33, p=0.02). Local and distant recurrence more likely if management was outside a specialist centre (RR:2.33, p=0.02; RR:1.77, p=0.01) and/or outside a cancer network (RR:2.32, p=0.02; RR:1.87, p=0.04). Local recurrence was less likely if a patient was evaluated by an MDT before surgery (RR:0.52, p=0.02). Distant recurrence was more likely to occur in those evaluated by an MDT after surgery (RR:1.64, p=0.04). Authors' conclusions: The development ofa treatment strategy within a formal multidisciplinary staff and treatment within a cancer network are both important prognostic factors for optimal clinical care.	MDTs consisted of weekly meetings of at least one radiologist, pathologist, surgeon, medical oncologist and clinical oncologist. 2 specialist centres were identified in this study, a University hospital and a comprehensive cancer centre. Mean or median follow up not reported but follow up was in the range 8–20 months for survivors. This is unlikely to be long enough to capture the majority of recurrences.	

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Bauer *et al.* (2001)	To report on adult patients with STS of the extremities or trunk wall diagnosed 1986–1997 and reported from all tertiary referral centres in Norway and Sweden.	Retrospective case series (population based).	1851 adults (=16 yrs) with STS of the extremity or trunk-wall entered onto the SSG register between 1986 and 1997. Head & neck, retroperitoneal and visceral sites were excluded as were KS and DFP. NORWAY, SWEDEN	Comparisons made for primary surgical treatment at sarcoma centre vs. elsewhere for the following: • Biopsy and imaging before surgery • surgical procedures • surgical margins • local recurrence.	Specialist tumour centres defined as those offering MDT management for sarcoma. Outcomes reported (other centre vs. specialist sarcoma centres). • CT or MRI of primary lesion before surgery: 35% vs. 80% • Biopsy before surgery: 55% vs. 6% • Wide or compartmental margin achieved: 11% vs. 66% • Cumulative 5 year local recurrence rate: 0.7 vs. 0.2	Overlap of cases with Gustavson (1994) and Trovik (2000).	3++
Wiklund *et al.* (1996)	To report patient outcomes following the establishment of an MDT for STS.	Retrospective case series.	134 patients with primary STS of the trunk or extremities. Patients were referred between 1987 and 1993 to an STS MDT. FINLAND	Local recurrence, disease free survival and amputation rate. Prognostic factors: tumour site, grade, depth, compartment and size.	STS MDT was defined as: Oncologists, radiotherapists, orthopaedic surgeons, plastic surgeons, pathologists and radiologists. MDT meetings were held weekly to discuss new cases, to review ongoing cases. The MDT handled approximately 2 new STS and 2 benign tumours weekly, typically discussing around 10 cases at each meeting. Local recurrence rate: 18/134 (13%) (median follow up 36 months) vs. 48% (Finnish population data 1960–1969). 3 year disease free survival: 69% vs. 36% (data from the same institution 1965–1975 prior to the STS MDT). Amputation rate: 12/104 (12%) for MDT managed patients vs. 10% (Finnish population data 1960–1969). Authors' conclusions: Improved results were seen in the institution	Historical data are compared to MDT data, without adjustment for prognostic factors or changes in treatment practices. The MDT served a population of approximately 1.5 million.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					since establishment of STS MDT. Handling 10 cases per week is probably close to the minimum required to justify the MDT.		
Stiller *et al.* (2000)	To calculate population based survival rates for osteosarcoma and Ewing's sarcoma among patients younger than 40 years, and to identify prognostic factors related to patterns of care.	Retrospective cohort study.	2843 people with malignant bone tumours diagnosed at age 0–39 years in the UK, 1980–1994. Patients were identified through the NCRT, English regional cancer registries and Scottish and Welsh national cancer registries. The UKCCSG and specialist bone tumour registries were also checked. Lists of patients entered in osteosarcoma and Ewing's sarcoma trials were supplied by the MRC cancer trials office and the UKCCSG. UK	Overall survival.	Multivariate survival analyses (Cox proportional hazards analysis) were carried out separately for patients with osteosarcoma (n=1297) and Ewing's sarcoma of bone (n=831). Variables included in the analysis: sex, age, tumour site, year of diagnosis and treatment centre type. Treatment centres were classified as BTS (bone tumour service), UKCCSG, OTH (other teaching hospitals), or NTH (non-teaching hospitals). Osteosarcoma RR (95% CI): • BTS 1 (reference) • UKCCSG 0.72 (0.57–0.92) • OTH 1.10 (0.90–1.34) • NTH 1.33 (1.03–1.71) • Unknown 1.15 (0.83–1.59) For patients with osteosarcoma survival was significantly better for those treated at UKCCSG centres than at the 2 supraregional bone tumour service (BTS) units. Survival was significantly poorer for those treated at non-teaching hospitals than at the BTS or UKCCSG centres. Ewing's sarcoma RR (95% CI): • BTS 1 (reference) • UKCCSG 1.06 (0.78–1.44) • OTH 1.40 (1.04–1.88) • NTH 1.83 (1.30–2.59) • Unknown 1.46 (0.91–2.35)	Only a subset of the results is presented in this appraisal. There were 2 bone tumour service units, the NSCAG designated units at Birmingham and London. The UKCCSG centres corresponded to the 20 paediatric oncology units affiliated with the UKCCSG. There were 26 teaching hospitals and 82 non-teaching hospitals. Disease stage not included as a prognostic factor.	2+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					For patients with Ewing's sarcoma survival was significantly better for those treated at BTS and UKCCSG centres than both teaching and non-teaching hospitals. Authors' conclusions: The results of this study suggest that survival from osteosarcoma and Ewing's sarcoma would be improved if more patients were treated at specialist bone tumour treatment centres and paediatric oncology centres.		

Table 4.b Does hospital case volume have an effect on outcomes for patients with sarcoma?

Abbreviations: CI, confidence interval; MRC, Medical Research Council; NRCT, National Register of Childhood Tumours; NSCAG, National Specialist Commissioning Advisory Group; RR, relative risk; STS, soft tissue sarcoma; UKCCSG, United Kingdom Children's Cancer Study Group.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Nijhuis *et al.* (2001)	To analyse how well national diagnostic guidelines for STS are being used in one region of Holland.	Retrospective observational study – clinical audit.	351 STS patients 1989–96. Exclusions: gastrointestinal STS, urogenital STS, Kaposi sarcoma. Patients were identified from a population based registry. NETHERLANDS	Adherence to diagnostic and referral guidelines. Adequacy of biopsy vs. case volume.	Adherence to guidelines significantly better in specialist centre. In district hospitals, patient volume had no significant influence on compliance with guidelines, except for management of patients with STS >3cm. In district hospitals, where fewer than 15 patients were treated in 7 years, significantly more often an inadequate biopsy procedure or even no biopsy was performed prior to resection. Older patients (>60 years) were significantly more often not referred to a specialist centre. Authors' conclusions: In many aspects of the diagnostic process of STS, existing guidelines were not followed, especially in community hospitals. Adherence to all individual guidelines was significantly better in the specialised centre. Concentration of patients with STS in a limited number of hospitals and intensified collaboration with specialised centres seem advisable.	It is not clear how the specialised sarcoma centre identified in the study qualified for this status (by consensus?).	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Paszat *et al.* (2002)	1. To describe STS of the extremities case volumes of hospitals and cancer centres (to provide a surrogate measure of specialised expertise); 2. to describe the proportion of cases admitted to hospitals with the largest experience in treatment of STS of the extremities and the proportion of cases of STS of the extremities that attend a multidisciplinary cancer centre (as a surrogate measure of multidisciplinary care) and 3. to describe the treatment of newly diagnosed STS of the extremities and clinical outcomes, in relation to institutional case volume.	Population-based retrospective case series.	1467 cases of extremity STS 1987–1996 in one Canadian province (Ontario). All patients aged 17 years or older. Data obtained from cancer registry, Canadian Institute for Health Information, and Radiation Oncology Research Unit database of radiation therapy records. CANADA	Overall survival; amputation or resection at any time during follow up after definitive surgery (surrogate measure of locally recurrent STS).	Using multivariate analysis the relative risk of death was 1.4 (95% CI 1.1–1.7) for patients who did not attend a multidisciplinary cancer centre within 3 months of diagnosis. The relative risk of amputation was 3.5 (95% CI 1.6–7.5) for patients who did not attend a multidisciplinary cancer centre within 3 months of diagnosis. Case volume of the hospital providing definitive treatment was not statistically associated with risk of amputation or death. Authors' conclusions: Cases not seen at a multidisciplinary cancer centre within 3 months following diagnosis of STS have an increased risk of amputation or death due to any cause.	Authors conclude that cases not seen at a multidisciplinary cancer centre within 3 months following diagnosis of STS have an increased relative risk for amputation at any time, and for death due to any cause. No clear definition of what constitutes a specialist centre. The timing of each death was not recorded (survival of 1 year and 5 years would have been coded the same).	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Stiller *et al.* (2000)	To calculate population based survival rates for osteosarcoma and Ewing's sarcoma among patients younger than 40 years, and to identify prognostic factors related to patterns of care.	Retrospective cohort study.	2843 people with malignant bone tumours diagnosed at age 0–39 years, in the UK, 1980–1994. Patients were identified through the NRCT, English regional cancer registries and Scottish and Welsh national cancer registries. The UKCCSG and specialist bone tumour registries were also checked. Lists of patients entered in osteosarcoma and Ewing's sarcoma trials were supplied by the MRC cancer trials office and the UKCCSG. UK	Overall survival.	Multivariate survival analyses (Cox proportional hazards analysis) were carried out separately for patients with osteosarcoma (n=1297) and Ewing's sarcoma of bone (n=831). Variables included in the analysis: sex, age, tumour site, year of diagnosis and centre size. Centre size was categorized according to the average annual number of new patients with osteosarcoma or Ewing's sarcoma (=10, 5–9, 2–4 or 0–1). Osteosarcoma RR (95% CI): • =10: 1 (reference) • 5–9: 0.84 (0.66–1.06) • 2–4: 0.99 (0.90–1.40) • 0–1: 1.12 (0.90–1.40) • Unknown: 1.08 (0.79–1.49) Ewing's sarcoma RR (95% CI): • =10: 1 (reference) • 5–9: 1.39 (1.03–1.87) • 2–4: 0.99 (0.74–1.32) • 0–1: 1.79 (1.33–2.42) • Unknown: 1.38 (0.87–2.21) Authors' conclusions: Survival from osteosarcoma and Ewing's sarcoma would be improved if more patients were treated at specialist bone tumour centres and paediatric oncology centres.	Only a subset of the results is presented in this appraisal, see other evidence tables. A significant effect of centre size was seen for Ewing's sarcoma but not for osteosarcoma. The only 2 centres with >10 patients per year were the supraregional (NSCAG) bone tumour units in Birmingham and London. Disease stage and tumour size were not included as a prognostic factor. Treatment centre was defined as the unit where initial planned treatment was received. Possibility of onward referral to specialist units of treatment failures, however.	2+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
(van Dalen 2000)	To investigate the influence of surgical experience on survival in retroperitoneal STS.	Case series.	Population based case series of 143 patients with retroperitoneal STS diagnosed between 1989 and 1994. Series included: 54 liposarcoma, 42 leiomyosarcoma and 10 MFH. 123 patients had surgical treatment and 20 patients did not. 52 (36%) patients were misdiagnosed preoperatively and originally treated for other assumed conditions. NETHERLANDS	Overall survival and completeness of tumour resection.	Surgical volume of hospital was dichotomised: =1 patient per year vs. <1 patient per year (on average). 35 patients were treated at 'high volume' (defined as at least 1 patient per year) hospitals and 108 treated elsewhere. Overall survival: In a univariate analysis (log rank test) patients who were treated in a 'higher volume' hospital did not have a better prognosis (p=0.96). A correct preoperative diagnosis was not associated with survival (p=0.69). In a multivariate analysis (Cox regression) independent factors associated with improved survival were an R0/R1 resection, low malignancy grade and the absence of distant metastases. Hospital surgical volume was eliminated from the Cox regression as a prognostic factor (p>0.10). Radical resection: Extent of surgery was dichotomised: complete resection (R0/R1) vs. no complete resection (R2/no surgery). Treatment in a higher volume hospital was not related to completeness of resection in univariate analysis (p=0.26) but in a multivariate analysis it was an independent predictor of completeness of resection (p=0.0004). Fixation of tumour was the other predictor of completeness of surgery (p<0.0001). Author's conclusions: There was a higher chance of obtaining a radical resection in higher surgical volume hospitals, but did not find a better long-term outcome in these patients.	Author notes that one patient annually is probably not the correct cut-off point to consider a treating surgeon as experienced. Unclear how hospital volume related to surgeon volume in this study; different surgeons could have been operating from case to case. Not reported whether preoperative misdiagnosis was more likely in low volume centres. Event rate probably too low for the number of factors considered in the prognostic model.	3+

Table 4.c Is there any evidence that a 'hub and spoke' structure for delivery of care affects outcome for patients with cancer?

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Michaels *et al.* (2000)	To evaluate the cost and quality implications of different possible organisational models for sub-specialist vascular services.	Systematic review and other techniques (modelling, local activity analysis, utility analysis, and decision analysis).	The study was based on the population requiring vascular services in the North Trent region. UK	Mortality, amputation, symptom severity, quality of life, patient preference, resource use, costs and cost effectiveness.	Analysis showed a strong patient preference for the availability of local treatment. Modelling demonstrated that centralisation of services would be expected to lead to improved outcomes but with an increase in overall resource requirements and the cost-effectiveness of some of the changes was estimated. Authors' conclusions: There is a need to rationalise services, taking into account the demonstrated clinical benefits of sub-specialisation and the patient preferences for local services. The compromise of 'hub and spoke' arrangements seems likely to best achieve this. Such an arrangement would also be relatively straightforward to achieve through a staged reconfiguration of services.	Vascular services cover a range of procedures some of which can be safely carried out in smaller hospitals (how applicable is this to sarcoma?).	2++
Ferguson (1996)	To review the literature regarding accessibility and centralisation of cancer services in the light of the Calman-Hine report.	Systematic review and questionnaires to local health authorities in the Yorkshire region.	57 studies relating to accessibility and patient utilisation of services (not restricted to cancer services).	Distance and utilisation of: • primary care • A&E • clinics & day cases • inpatients • visitors • screening. Distance and: • willingness to travel • mortality and morbidity.	3000 articles were identified and approximately 300 were screened against inclusion criteria of relevance, outcome and design. 243/300 papers were rejected. The quality of the evidence was generally poor with a lack of properly controlled trials. Direct evidence of the relationship between distance and mortality or morbidity was rare, although 2 studies of cancer patients indicated that outcomes are not affected by distance. 2 studies reported that patients are willing to travel some distance to overcome delays in accessing hospital services. There is some evidence that use of diagnostic services may be more sensitive than treatment services to distance effects, patients being more willing to travel for treatment services.	Medline and 'other databases' searched, including those indexing unpublished studies. Researchers were also contacted for unpublished data. No language restriction. Studies relating to less developed countries or to mental health services were excluded. A wide range of studies are included across many countries, healthcare settings and patient groups.	2+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					The author concludes that "Overall the research evidence on the accessibility and centralisation trade-off is of relatively poor quality. There is some evidence both from the literature and from discussions with local purchasers that patients - once diagnosed as having cancer - will overcome sometimes considerable access difficulties."		

Treatment of patients with sarcoma

Patients with bone sarcoma

The question

a) Are outcomes (local control, surgical margins, patient experience and survival) better for people with suspected bone sarcoma treated in specialist sarcoma units than for those treated in non-specialist units?

Nature of the evidence

a) Are outcomes (local control, surgical margins, patient experience and survival) better for people with suspected bone sarcoma treated in specialist sarcoma units than for those treated in non-specialist units?

The UK cohort study of Stiller and co-workers (Stiller *et al.* 2000) included a partially case mix adjusted analysis comparing the overall survival of people younger than 40 years with bone sarcoma initially treated at specialist centres with those treated elsewhere. Specialist centres were NSCAG bone tumour treatment services or UKCCSG paediatric oncology centres, all other hospitals were considered non-specialist centres for the purposes of this evidence review.

An observational study (Bergh *et al.* 2001) of Swedish people with pelvic or axial chondrosarcoma reported case-mix adjusted analyses of the overall and disease-free survival of patients treated at a specialist centre and at non-specialist centres. The specialist unit was defined as a tumour centre with expertise in the treatment of bone and soft tissue tumours and the comparison group was patients referred to the unit after receiving their primary treatment outside a tumour centre.

A small Australian observational study (Pollock & Stalley 2004) of people with musculoskeletal tumours (both bone and soft tissue) compared the surgical margins achieved by specialist unit. The specialist unit was the musculoskeletal tumour service of an orthopaedic surgery department. The comparison group was patients referred to the specialist unit following primary surgery elsewhere.

No relevant studies reporting comparisons of local control or patient experience were identified.

Summary of the supporting evidence for the recommendations

a) Are outcomes (local control, surgical margins, patient experience and survival) better for people with suspected bone sarcoma treated in specialist sarcoma units than for those treated in non-specialist units?

The limited evidence suggested that overall survival was better for patients treated in specialist centres. In the UK cohort study (Stiller *et al.* 2000) people with Ewing's sarcoma or osteosarcoma initially treated at specialist centres had better overall survival than those treated elsewhere.

The other two studies (Pollock & Stalley 2004; Bergh *et al.* 2001) used patients referred to specialist centres following treatment elsewhere as a comparison group and could be subject to bias since this group could include more difficult cases.

The Swedish study reported better overall survival in patients treated at a specialist centre (Bergh *et al.* 2001). Patients who had their initial surgery outside a specialist centre also had an increased risk of an incomplete surgical resection and local recurrence.

The Australian study (Pollock & Stalley 2004) reported that patients initially treated at a specialist centre were more likely to receive a complete surgical removal of their tumour.

Table 5 Are outcomes better for patients with suspected bone sarcoma treated in specialist sarcoma units than for those treated in non specialist units.

Abbreviations: CI, confidence interval; MRC, Medical Research Council; NRCT, National Register of Childhood Tumours; NSCAG, National Specialist Commissioning Advisory Group; RR, relative risk; UKCCSG, United Kingdom Children's Cancer Study Group.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Stiller *et al.* (2000)	To calculate population based survival rates for osteosarcoma and Ewing's sarcoma among patients younger than 40 years, and to identify prognostic factors related to patterns of care.	Retrospective cohort study.	2843 people with malignant bone tumours diagnosed at age 0–39 years in the UK, 1980–1994. Patients were identified through the NCRT, English regional cancer registries and Scottish and Welsh national cancer registries. The UKCCSG and specialist bone tumour registries were also checked. Lists of patients entered in osteosarcoma and Ewing's sarcoma trials were supplied by the MRC cancer trials office and the UKCCSG. UK	Overall survival.	Multivariate survival analyses (Cox proportional hazards analysis) were carried out separately for patients with osteosarcoma (n=1297) and Ewing's sarcoma of bone (n=831). Variables included in the analysis: sex, age, tumour site, year of diagnosis and treatment centre type. Treatment centres were classified as BTS (bone tumour service), UKCCSG, OTH (other teaching hospitals), or NTH (non-teaching hospitals). Osteosarcoma RR (95% CI): • BTS 1 (reference) • UKCCSG 0.72 (0.57–0.92) • OTH 1.10 (0.90–1.34) • NTH 1.33 (1.03–1.71) • Unknown 1.15 (0.83–1.59) For patients with osteosarcoma survival was significantly better for those treated at UKCCSG centres than at the 2 supraregional bone tumour service (BTS) units. Survival was significantly poorer for those treated at non-teaching hospitals than at the BTS or UKCCSG centres. Ewing's sarcoma RR (95% CI): • BTS 1 (reference) • UKCCSG 1.06 (0.78–1.44)	A subset of the results is presented in this appraisal, see other evidence tables. There were 2 bone tumour service units, the NSCAG designated units at Birmingham and London. The UKCCSG centres corresponded to the 20 paediatric oncology units affiliated with the UKCCSG. There were 26 teaching hospitals and 82 non-teaching hospitals. Disease stage not included as a prognostic factor.	2+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					• OTH 1.40 (1.04–1.88) • NTH 1.83 (1.30–2.59) • Unknown 1.46 (0.91–2.35) For patients with Ewing's sarcoma survival was significantly better for those treated at BTS and UKCCSG centres than both teaching and non-teaching hospitals. Authors' conclusions: The results of this study suggest that survival from osteosarcoma and Ewing's sarcoma would be improved if more patients were treated at specialist bone tumour treatment centres and paediatric oncology centres.		
Bergh *et al.* (2001)	To assess the outcome of patients with pelvic, sacral or spinal chondrosarcoma treated at a tumour centre by using modern, aggressive surgical techniques and to identify prognostic factors.	Retrospective case series.	Sixty-nine consecutive patients with chondrosarcoma of the pelvis (46 cases), sacrum (11 cases), and mobile spine (12 cases) who were treated at a University Hospital Musculoskeletal tumour centre from 1967 to 1999. SWEDEN	Local recurrence, metastasis and tumour-related death.	52/69 patients had their primary surgery at the tumour centre, 10/69 patients had primary surgery outside the tumour centre and 7 patients did not have surgery (metastatic or unresectable disease). 6/52 primary resections in the tumour centre were intralesional (R2) compared to 10/10 of those outside the centre, (11% vs. 100%, RR: 0.11). 36/52 primary resections in the tumour centre had wide margins (R0) compared to 0/10 of those outside the centre, (69% vs. 0%). Local recurrence occurred following (at most) 12/52 primary resections in the tumour centre and (at least) 5/10 primary resections outside the centre (23% vs. 50%, RR: 0.46). Using multivariate analysis, primary treatment outside the tumour centre was an adverse prognostic factor for local recurrence ($p<0.01$) and tumour-related death ($p<0.01$). Other factors associated with a worse prognosis with respect to local control were high histologic tumour grade,	Some of the cases reported were treated more than 30 years ago. Specialist centre not explicitly defined, authors refer to “a tumour centre with expertise in the treatment of bone and soft tissue tumours". Inadequate event rate (too few deaths or recurrences) for the number of variables in the multivariate analysis. Patients referred after primary surgery elsewhere more likely to be complicated cases (biased towards incomplete resections and locally recurrent disease). The number of patients treated successfully outside the centre is not reported in this paper.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					increasing patient age, incisional biopsy versus a non-invasive diagnostic procedure, and inadequate surgical margins. Authors' conclusions: Centre-based diagnosis and treatment using modern aggressive surgical techniques significantly improve the prognosis of patients with chondrosarcoma of the pelvis, sacrum and spine.	Mean overall follow up was 10.6 years (range 0.2 to 32 years). This case series, consisting of pelvic and axial chondrosarcomas, represented a group requiring particularly complex surgical treatment.	
Pollock & Stalley (2004)	To examine the early management of patients biopsied for musculoskeletal tumours.	Prospective case series.	All patients (n=144) referred to the musculoskeletal tumour service of an Orthopaedic Surgery Department during 2002. 48 malignant and 35 benign bone tumours; 29 malignant and 30 benign soft tissue tumours. AUSTRALIA	Alterations in treatment and patient outcomes following biopsy either in a referring institution or a recognised treatment centre.	Comparisons are between outcomes at musculoskeletal tumour service and referring institutions: • Suboptimal biopsy site significantly hindering definitive treatment: 2/113 vs. 11/29 (2% vs. 38%, RR: 0.05, p<0.01). • Adequate material at biopsy: 110/113 vs. 21/29 (97% vs. 72%, RR: 1.34, p<0.01). • Amputation rate (for malignant lesions): 3/57 vs. 4/20 (7% vs. 25%, RR: 0.28, p<0.03). • Incomplete resection (for malignant lesions) requiring re-resection: 2/57 vs. 8/40 (4% vs. 40%, RR: 0.10, p<0.0001) Authors' conclusions: There is a high complication rate when patients with musculoskeletal tumours are biopsied by surgeons inexperienced in their management. These patients are better served by early referral to a specialist centre where staging investigations can be performed with minimal morbidity.	Authors have considered the effect of selection bias - the patients referred could be difficult diagnostic cases, but the analysis is not case-mix adjusted.	3+

Patients with limb, limb girdle or truncal STS

The question

a) Are outcomes (surgical margins, local control, patient experience and survival) better for people with suspected limb, limb girdle or truncal STS treated in specialist sarcoma units than for those treated in non-specialist units?

Nature of the evidence

a) Are outcomes (surgical margins, local control, patient experience and survival) better for people with suspected limb, limb girdle or truncal STS treated in specialist sarcoma units than for those treated in non-specialist units?

Surgical Margins

Six observational studies, from the UK (Bhangu *et al.* 2004), Australia (Pollock & Stalley 2004), France (Ray-Coquard *et al.* 2004) and Sweden (Rooser *et al.* 1987; Skytting *et al.* 1999; Rooser *et al.* 1987; Rydholm *et al.* 1983), reported comparisons of surgical margins in specialist and non-specialist settings. Two studies, from the UK (Goodlad *et al.* 1996) and USA (Randall *et al.* 2004), reported a comparison of specialist and non-specialist determination of surgical margins in STS.

Specialist treatment setting was defined in the following ways: an MDT involved in managing sarcomas and located in a sarcoma treatment centre (Bhangu *et al.* 2004; Rydholm *et al.* 1983); formal pre-operative evaluation by a multidisciplinary team in a secondary or tertiary setting (Ray-Coquard *et al.* 2004); the musculoskeletal tumour service of an orthopaedic surgery department (Pollock & Stalley 2004); a musculoskeletal tumour service (Rooser *et al.* 1987); an STS clinic (Goodlad *et al.* 1996); the sarcoma service of a tertiary medical centre (Randall *et al.* 2004) and a Scandinavian Sarcoma Group treatment centre (Skytting *et al.* 1999).

Studies used the following groups for comparison with patients treated in the specialist setting: patients treated in district general hospitals without a sarcoma

MDT (Bhangu *et al.* 2004); patients referred to a musculoskeletal tumour service following treatment elsewhere (Pollock & Stalley 2004); patients not formally reviewed by a sarcoma MDT (Ray-Coquard *et al.* 2004) and patients treated in non-specialist hospitals (Rooser *et al.* 1987; Skytting *et al.* 1999; Rydholm *et al.* 1983).

Study populations included people with: limb, limb girdle or truncal STS (Bhangu *et al.* 2004; Rooser *et al.* 1987); primary STS (the majority of patients having limb or truncal tumours) (Ray-Coquard *et al.* 2004; Randall *et al.* 2004; Goodlad *et al.* 1996); bone or soft tissue tumours of the limb, limb girdle, trunk, spine or pelvis (Pollock & Stalley 2004) and limb, limb girdle or truncal synovial sarcoma (Skytting *et al.* 1999).

Local recurrence

Four observational studies, from the UK (Bhangu *et al.* 2004), Sweden (Gustafson *et al.* 1994), Finland (Wiklund *et al.* 1996) and France (Ray-Coquard *et al.* 2004), included comparisons between the local recurrence of STS in people treated in specialist and non-specialist settings. None of these analyses was adjusted for case mix.

The Finnish study (Wiklund *et al.* 1996) compared local recurrence in people with limb, limb girdle or truncal STS treated by a specialist sarcoma MDT with population based figures. The characteristics of the other studies are described in the previous section.

A Canadian study (Paszat *et al.* 2002) used resection or amputation (at the primary site) during follow up after primary surgery as a surrogate measure of local recurrence in people with limb STS treated in specialist and non-specialist settings. Partial adjustment was made for case mix in this study. The specialist treatment group was those patients who received a formal pre-operative evaluation at a multidisciplinary cancer centre, and the comparison group was patients who were not referred to such a centre.

Minimum follow up of surviving patients in the studies was: five years (Bhangu *et al.* 2004); three years (Gustafson *et al.* 1994); less than one year (Ray-Coquard *et al.* 2004; Wiklund *et al.* 1996) and not stated (Paszat *et al.* 2002).

Overall survival

Four observational studies, from the UK (Bhangu *et al.* 2004; Stiller 1988), Sweden (Gustafson *et al.* 1994) and Canada (Paszat *et al.* 2002), included comparisons of the overall survival of patients treated in specialist and non-specialist settings. Two studies adjusted for case mix (Bhangu *et al.* 2004; Paszat *et al.* 2002) and two did not (Gustafson *et al.* 1994; Stiller 1988).

The study of Stiller (1988) reported a comparison of the overall survival of children with rhabdomyosarcoma treated in paediatric oncology centres with those treated at other teaching hospitals. The characteristics of the other studies are detailed in the two preceding sections.

Patient experience

No relevant studies were identified.

Summary of the supporting evidence for the recommendations

a) Are outcomes (surgical margins, local control, patient experience and survival) better for people with suspected limb, limb girdle or truncal STS treated in specialist sarcoma units than for those treated in non-specialist units?

Surgical margins

The recommendation that surgery should be performed in specialist centres is supported by evidence that adequate surgical margins are more likely when initial surgery for STS is performed in a specialist treatment centre. Five of the six relevant studies (Pollock & Stalley 2004; Ray-Coquard *et al.* 2004; Rooser *et al.* 1987; Rydholm *et al.* 1983; Skytting *et al.* 1999) found adequate surgical margins were more likely for patients treated at specialist centres.

The UK study (Bhangu *et al.* 2004) did not observe a difference between the adequacy of surgical margins at specialist and non-specialist centres. A difference in the case mix of the two groups was evident; patients treated at the specialist centre were more likely to have large and deep tumours.

Caution should be exercised, however, as none of these studies was case mix adjusted. There is also the issue of the accuracy of surgical margin determination in specialist and non-specialist settings. Two studies reported that specialist review often reveals residual disease after a supposedly wide resection at a non-specialist centre (Goodlad *et al.* 1996; Randall *et al.* 2004).

Local recurrence

There is consistent evidence, from four observational studies (Bhangu *et al.* 2004; Gustafson *et al.* 1994; Ray-Coquard *et al.* 2004; Wiklund *et al.* 1996) that local recurrence of sarcoma is less likely when the initial surgery is performed at a specialist treatment centre. None of these studies adjusted for case mix, however. In a partially case mix adjusted study (Paszat *et al.* 2002), using surrogate measures of local recurrence, patients not attending a multidisciplinary cancer centre were at greater risk of local recurrence.

Overall survival

The studies which adjusted for case mix (Bhangu et al. 2004; Paszat et al. 2002) reported that people with STS treated at specialist centres have better overall survival than those treated elsewhere. Comparisons that were unadjusted for case mix (Bhangu et al. 2004; Gustafson et al. 1994), however, did not report a survival advantage for those treated at specialist centres. The discrepancy between adjusted and unadjusted comparisons suggests a greater proportion of patients with poor prognosis among those treated at specialist centres than among those treated at non-specialist centres.

Patient experience

No relevant studies reporting patient's perspectives on specialist and non-specialist treatment settings were identified.

Table 6 Are outcomes (surgical margins, local control, patient experience and survival) better for people with suspected limb, limb girdle or truncal STS treated in specialist sarcoma units than for those treated in non-specialist units?

CCRG, Childhood Cancer Research Group; CI, confidence interval; DGH, district general hospital; HR, hazard ratio; RHA, regional health authority; RR, relative risk; STS, soft tissue sarcoma; UKCCSG, United Kingdom Children's Cancer Study Group.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Bhangu *et al.* (2004)	To investigate whether there is evidence that patients with STS do better if treated in a specialist centre compared with DGHs.	Retrospective case series.	263 patients diagnosed and treated with curative intent for STS 1994–1996 in one RHA. Patients were treated in a specialist centre (SC) (n=96) or at 1 of 38 DGHs (n=164). Follow up min 5 years. Exclusions: KS, head and neck, retroperitoneal tumours. UK	Overall survival; local recurrence.	Adequate excision margins: DGH 35%, SC 39%. Univariate analysis (log-rank test) showed no significant difference between the 2 settings in local recurrence and overall survival. 5 years local recurrence rate: DGH 39%, SC 19%. Overall 5 year survival rate of non-metastatic patients: 58% in both settings. Multivariate analysis (Cox regression) showed patients treated at the SC had a small survival advantage (HR: 0.59; 95% CI: 0.35–0.99) taking into account age and tumour size, depth and grade. Authors' conclusions: Centralisation of treatment improves local control in all patients with sarcoma and survival in some.	Specialist centre (SC) defined as 'unit with MDT managing sarcomas'. Patients treated initially at DGHs for small lumps but subsequently referred to SC due to post-operative diagnosis analysed in SC set. Patients treated at SC tended to be younger with larger tumours with a greater proportion of both deep and high-grade tumours. Metastatic patients excluded from analysis.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Goodlad *et al.* (1996)	To examine the excision margins of patients referred to an STS clinic following presumed complete excision of their primary tumour elsewhere.	Case series.	95 patients referred to an STS clinic following presumed complete excision of their primary tumour elsewhere. These 95 patients had surgical margins less than 1cm from the nearest edge of the sarcoma and were re-resected. Patients with clinically obvious recurrence or retroperitoneal tumours were excluded. UK	Adequacy of original surgical margins. Adequacy of re-resection margins.	Adequacy of surgical margins (considered complete by referring surgeons): 39/95 (41%) adequate. Adequacy of re-resection margins (at STS clinic): 48/95 (51%) adequate. Granulation or scar tissue from the initial operation extending to re-resection margins was responsible for 31/47 inadequate margins. Authors' conclusions: Surgical assessment of the accuracy of excision is very inaccurate. The large number of patients who had inadequate initial treatment emphasises the need for a co-ordinated multidisciplinary approach to the management of patients with STS.	Patients had been referred following treatment elsewhere (may not be representative of patients with STS in general). Data not analysed statistically.	3-
Gustafson *et al.* (1994)	To analyse the quality of surgery in a population-based series of patients with primary STS of the extremity and trunk wall.	Retrospective case series.	375 patients with STS of the extremity (n=329) and trunk wall (n=46). All patients were diagnosed between 1970 and 1989 and identified from a population based registry. SWEDEN	Overall survival, local recurrence and total number of operations performed for the primary tumour.	Patients were either referred to a specialist STS tumour centre before initial surgery (n=195), after surgery elsewhere (n=102), or not referred after initial surgery elsewhere (n=78). Minimum follow up was 3 years for survivors. In patients referred before surgery: disease specific survival was 74%, local recurrence was 18%; mean number of operations per tumour was 1.12. In patients referred immediately after surgery elsewhere: disease specific survival was 77%, local recurrence was 23%; mean number of operations per tumour was 1.95. In patients not referred after surgery elsewhere: disease specific survival was 69%, local recurrence was 45%; mean number of operations per tumour was 1.58.	Conventional survival analysis (e.g. Kaplan - Meier) would have been more useful. Incisional biopsy was classified as an operation whereas fine-needle aspiration biopsy was not. Patients referred after surgery or not referred had smaller and more often subcutaneous tumours. Patients referred directly to centre had a poorer prognosis to start with; this bias would lead to underestimation of the benefit of treatment at a specialist centre.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					The difference between groups was significant (using Chi squared) for recurrence rate ($p<0.01$) and number of operations ($p<0.01$). Local recurrence for patients referred before surgery vs. patients not referred (18% vs. 45%, RR: 0.4). Disease specific survival for patients referred before surgery vs. not referred (77% vs. 69%, RR: 1.12). Authors' conclusions: Findings show that patients with STS should be treated at a tumour centre, and that they should be referred before surgery.		
Paszat *et al.* (2002)	1. To describe STS of the extremities case volumes of hospitals and cancer centres (to provide a surrogate measure of specialised expertise) 2. to describe the proportion of cases admitted to hospitals with the largest experience in treatment of STS of the extremities and the proportion of cases of STS of the extremities that attend a multidisciplinary cancer centre (as	Population-based retrospective case series.	1467 cases of extremity STS 1987–1996 in one Canadian province (Ontario). All patients aged 17 years or older. Data obtained from cancer registry, Canadian Institute for Health Information, and Radiation Oncology Research Unit database of radiation therapy records. CANADA	Overall survival; amputation; amputation or resection at any time during follow up after definitive surgery (surrogate measure of locally recurrent STS).	Using multivariate analysis the relative risk of death was 1.4 (95% CI 1.1–1.7) for patients who did not attend a multidisciplinary cancer centre within 3 months of diagnosis. The relative risk of amputation was 3.5 (95% CI 1.1–1.7) for patients who did not attend a multidisciplinary cancer centre within 3 months of diagnosis. Case volume of the hospital providing definitive treatment was not statistically associated with risk of amputation or death. Authors' conclusions: Cases not seen at a multidisciplinary cancer centre within 3 months following diagnosis of STS have an increased risk of amputation or death due to any cause.	Authors conclude that cases not seen at a multidisciplinary cancer centre within 3 months following diagnosis of STS have an increased relative risk for amputation at any time, and for death due to any cause. No adjustment made for case-mix. No clear definition of what constitutes a specialist centre. Reliability of cancer registry data? Study did not consider a number of potential prognostic factors including: disease stage; tumour grade and site; treatment characteristics. The timing of each death was not recorded (survival of 1 year and 5 years would have been coded the same). May not be directly applicable to the UK setting, the MDT cancer centres described in this study provide medical	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
	a surrogate measure of multidisciplinary care) 3. to describe the treatment of newly diagnosed STS of the extremities and clinical outcomes, in relation to institutional case volume.					and clinical oncology services but not surgery.	
Pollock & Stalley (2004)	To examine the early management of patients biopsied for musculoskeletal tumours.	Prospective case series.	All patients (n=144) referred to the musculoskeletal tumour service of an Orthopaedic Surgery Department during 2002. 48 malignant and 35 benign bone tumours; 29 malignant and 30 benign soft tissue tumours. AUSTRALIA	Alterations in treatment and patient outcomes following biopsy either in a referring institution or a recognised treatment centre.	Comparisons are between outcomes at musculoskeletal tumour service and referring institutions: • Suboptimal biopsy site significantly hindering definitive treatment: 2/113 vs. 11/29 (2% vs. 38%, RR: 0.05, p<0.01). • Adequate material at biopsy: 110/113 vs. 21/29 (97% vs. 72%, RR: 1.34, p<0.01). • Amputation rate (for malignant lesions): 3/57 vs. 4/20 (7% vs. 25%, RR: 0.28, p<0.03). • Incomplete resection (for malignant lesions) requiring re-resection: 2/57 vs. 8/40 (4% vs. 40%, RR: 0.10, p<0.0001). Authors' conclusions: There is a high complication rate when patients with musculoskeletal tumours are biopsied by surgeons inexperienced in their management. These patients are better served by early referral to a specialist centre where staging investigations can be performed with minimal morbidity.	Authors have considered the effect of selection bias - the patients referred could be difficult diagnostic cases, but the analysis is not case-mix adjusted.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Ray-Coquard *et al.* (2004)	To assess the conformity of medical practice to clinical guidelines for the management of STS.	Observational study – retrospective clinical audit.	100 newly diagnosed STS patients seen between 1999 and 2001. Cases were drawn at random from a series of 650 in a single French region. Exclusions: tumours of bone, CNS and Kaposi sarcoma; metastases at diagnosis. FRANCE	Local and distant recurrence; resection margin. Conformity of management with clinical practice guidelines.	7% of cases had MDT review before biopsy and there were 42% pre-surgery biopsies. Conformity to guidelines was rated 52, 81, 94 and 95% for initial surgery, radiation therapy, chemotherapy and follow up respectively. R0 resections were more likely (15/35 vs. 10/60, 43% vs. 17%, RR: 2.35) and R2 resections less likely (7/35 vs. 36/60, 20% vs. 60%, RR: 0.33) if patients had an MDT evaluation before surgery. R2 resections were less likely in University or cancer hospitals than in general hospitals (27% vs. 61%, RR:0.44, p=0.02). At multivariate analysis, pre-surgery MDT discussion, management in specialist centre and management within cancer network independently predicted conformity to guidelines. Local relapse was more likely if surgery performed by non-specialist (RR:7.33, p=0.02). Local and distant recurrence more likely if management was outside a specialist centre (RR:2.33, p=0.02; RR:1.77, p=0.01) and or outside a cancer network (RR:2.32, p=0.02; RR:1.87, p=0.04). Local recurrence was less likely if a patient was evaluated by an MDT before surgery (RR:0.52, p=0.02). Distant recurrence was more likely to occur in those evaluated by an MDT after surgery (RR:1.64, p=0.04). Authors' conclusions: The development of a treatment strategy within a formal multidisciplinary staff and treatment within a cancer network are both important prognostic factors for optimal clinical care.	Risk of distant recurrence for those evaluated by an MDT before surgery is not reported. MDTs consisted of weekly meetings of at least one radiologist, pathologist, surgeon, medical oncologist and clinical oncologist. 2 specialist centres were identified in this study, a University hospital and a comprehensive cancer centre. Mean or median follow up not reported but follow up was in the range 8–20 months for survivors. This is unlikely to be long enough to capture the majority of recurrences.	3++

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Rooser *et al.* (1987)	To analyse the referral pattern and treatment of all patients with STS of the trunk and extremities within a defined area.	Retrospective case series.	94 patients with STS of the trunk and extremities in Sweden diagnosed in 1982. Excluded: metastatic disease; dermal sarcomas; non-surgery patients. SWEDEN	Resection margin.	38 (40.4%) patients had diagnosis and treatment at peripheral hospitals; 56 (59.6%) patients were referred to sarcoma treatment centres – 36 prior to surgery and 20 after marginal excision or incisional biopsy. R0 resection was more likely in sarcoma centres than in other hospitals (48/56 vs. 8/38, 80% vs. 20%, RR: 4). Authors' conclusions: The treatment of STS outside tumour centres is less than optimal, and centralisation is associated with substantially increased referral of patients with benign tumours to catch the majority of STS in the untouched state.	Study uses data from more than 20 years ago. Musculoskeletal tumour centre is not defined. In authors' centre, 10 patients with benign lesions were referred for every sarcoma patient with an untouched tumour. Cited as evidence of effectiveness of information to peripheral hospitals about indications for referral of patients with soft tissue lesions. A greater proportion of large deep tumours than small superficial tumours were referred to the centre before surgery. Thus the case mix of the centre likely to be biased towards advanced and high grade STS. This may lead to an underestimation of the relative effectiveness of surgery at the sarcoma centres. Results not analysed statistically.	3+
Rydholm *et al.* (1983)	To analyse the methods used in the diagnosis and treatment of STS, and variations of these methods over time and setting.	Retrospective case series.	261 patients with STS in trunk and extremities, treated between 1971 and 1981. Patients treated by specialist centre were separated into patients referred before and after surgery. SWEDEN	Resection margin and diagnostic accuracy.	In the period 1971–1980, 111/142 patients treated by the centre eventually had R0 (wide or compartmental) resection compared to 15/46 of the patients treated outside the centre (78% vs. 32%, RR: 2.44). Amputations (centre vs. other institutions) 15/142 vs. 13/46 (11% vs. 28%). When recorded, the tentative pre-operative diagnosis was false negative (benign) in 8/70 patients treated by the centre compared to 67/107 of the patients treated outside the centre (11% vs. 67%, RR:0.16). Over the years 1964–1981 the number of patients referred increased.	Some data in this study is 40 years old. Specialised sarcoma group (MDT?) defined as consisting of representatives from orthopaedic surgery, clinical pathology, clinical cytology, diagnostic radiology and oncology. Where there was uncertainty over surgical margins, the lower class was chosen. Statistical analysis is not used.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: Patients should be seen by a specialised group for 2 reasons. Firstly because clinical findings and imaging are more easy to interpret for an untouched tumour. Secondly marginal excision or incisional biopsy performed improperly may compromise the definitive surgery and lead to poorer outcomes.		
Skytting *et al.* (1999)	To identify clinical factors related to outcome in a case series of patients with synovial sarcoma.	Case series, prognostic study.	104 patients diagnosed with primary synovial sarcoma of the extremities or trunk wall (with no metastases at diagnosis). All patients were diagnosed between 1986 and 1994, and were identified from a national cancer registry. SWEDEN	Adequacy of surgical treatment. 5 year metastasis free survival.	Specialist treatment centres were assumed to be those belonging to the Scandinavian Sarcoma Group. Median follow up of survivors was 6 years (range 3–11 years). 34/104 patients developed metastases. Adequacy of surgical treatment (in specialist centre vs. other centre) was 74/88 vs. 5/16 (84% vs. 31%, p<0.01). Inadequate surgical treatment was not associated with reduced 5 year metastasis free survival. 5 year survival (treated in specialist centre vs. other centre) was 62/88 vs. 9/16 (71% vs. 50%). Other prognostic factors were investigated: tumour size, depth, location and compartment; patient's age and sex; surgical procedure. In a univariate Cox regression, treatment in a specialist centre was not significantly associated with metastasis free survival. Authors' conclusions: The poor results of surgery among patients treated outside of Scandinavian Sarcoma Group centres point to the importance of referral of patients with soft tissue tumours to sarcoma centres for treatment.	Small study, only 16 patients had surgery for their primary tumour outside a specialist centre. Primary treatment in a specialist centre was not a significant prognostic factor for overall survival on univariate analysis, but was not included as a factor in the multivariate analysis.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Stiller (1988)	To compare survival rates of UKCCSG and non-UKCCSG patients with 8 of the principal types of childhood neoplasm.	Case series.	Patients (n=3115) aged 14 or less entered onto the CCRG or UKCCSG registries between 1977 and 1984. Patients had one of eight of the principal types of childhood neoplasm. Patients entered onto the UKCCSG register were managed at paediatric oncology centres. UK	Overall survival.	Log rank tests were used to compare the survival curves of patients grouped by diagnosis, by year of diagnosis (1977–1980 vs. 1981–1984) and by treatment centre (paediatric oncology centres vs. other teaching hospitals vs. other non-teaching hospitals). Osteosarcoma For the period 1977–1980 there was similar survival in all types of treatment centre, with 3 year survival of around 36% and 5 year survival of about 30%. For the period 1981–1984 children treated at paediatric oncology centres showed a considerable improvement in survival (approximate 3 year survival 55%, 5 year survival 50%). Ewing's sarcoma A greater proportion of children survived at paediatric oncology centres. For 1981–1984 3 year survival at paediatric oncology centres was 50%, at other teaching hospitals 33% and at non-teaching hospitals 45% ($p<0.05$, log rank test). Rhabdomyosarcoma There was a higher proportion of survivors at paediatric oncology centres. For 1981–1984 3 year survival at paediatric oncology centres was 63%, and at other teaching hospitals 36% (insufficient data from non-teaching hospitals) ($p<0.01$, log rank test). Results were also presented for Hodgkin's disease, non-Hodgkin's lymphoma, Wilm's tumour, neuroblastoma and acute non-lymphoblastic leukaemia (but not included in this appraisal). Author's conclusions: Children with cancer should be referred to specialist centres so that they may benefit as early as possible from the latest advances in treatment.	Possibly outdated study. Not all statistical comparisons are reported. No adjustment for case mix (author notes that paediatric oncology centres treated a greater proportion of Ewing's sarcoma patients with poor prognosis). Follow up was shorter for the 1981–1984 group.	3+

Patients with abdominal or pelvic STS

The question

a) Are outcomes better for people with suspected abdominal or pelvic STS treated in specialist sarcoma units than for those treated in non specialist units?

Nature of the evidence

a) Are outcomes better for people with suspected abdominal or pelvic STS treated in specialist sarcoma units than for those treated in non specialist units?

Two studies including a comparison of patterns of care and outcome in people with retroperitoneal STS (RPSTS) were identified. The population-based observational study of 143 people in the Netherlands with RPSTS (van Dalen 2000) compared the outcomes of those managed by hospitals treating more than one patient a year on average with those managed at hospitals treating fewer patients. A later study of Dutch people with RPSTS by the same group (van Dalen *et al.* 2004) compared the survival and completeness of resection of 107 patients treated at a single tertiary referral centre "of excellence" with 124 patients treated elsewhere.

Due to limited direct evidence, institutional case series reporting outcomes in people with RPSTS were also included. In the absence of an accepted definition of what constitutes a specialist RPSTS treatment unit, case volume was used as a surrogate of specialisation. The proportion of patients with primary, recurrent and metastatic disease at presentation, tumour grade and median tumour size were extracted in the evidence table as crude indicators of the case mix of the study populations.

The case series included the following patient groups: people with localised RPSTS (Karakousis *et al.* 1995), people with RPSTS who were candidates for surgery (Mackenzie *et al.* 2003; Malerba *et al.* 1999; Pirayesh *et al.* 2001; van Doorn *et al.* 1994; Zornig *et al.* 1992), people with primary RPSTS (Gilbeau *et al.* 2002; Gronchi *et al.* 2004; Hassan *et al.* 2004; Ho *et al.* 1991; Kilkenny, III *et al.*

1996; Rossi *et al.* 1993; Stoeckle *et al.* 2001), all people with RPSTS regardless of disease stage or management (Bautista *et al.* 2000; Herman *et al.* 1999; Jenkins *et al.* 1996; Lewis *et al.* 1998; Makela *et al.* 2000; Singer *et al.* 1995; Youssef *et al.* 2002; Catton *et al.* 1994) people with retroperitoneal liposarcoma (Neuhaus *et al.* 2005; Singer *et al.* 2003), people with high grade RPSTS (Shiloni *et al.* 1993), and patients with their first recurrence following complete resection of RPSTS (Wang *et al.* 1994).

Summary of the supporting evidence for the recommendations

a) Are outcomes better for patients with suspected abdominal or pelvic STS treated in specialist sarcoma units than for those treated in non specialist units?

van Dalen and co-workers (van Dalen *et al.* 2004) observed better overall 5 year survival in patients treated at a specialist tertiary referral centre compared to those treated elsewhere. Complete surgical resection of RPSTS was also more likely in the tertiary referral centre. In the earlier study of van Dalen (van Dalen 2000) complete surgical resection of RPSTS was more likely at hospitals treating more than one such patient per year on average. In this study, however, overall survival was not related to case volume, in a case mix adjusted analysis.

In 25 institutional case series (Bautista *et al.* 2000; Catton *et al.* 1994; Gilbeau *et al.* 2002; Gronchi *et al.* 2004; Hassan *et al.* 2004; Herman *et al.* 1999; Ho *et al.* 1991; Jenkins *et al.* 1996; Karakousis *et al.* 1995; Kilkenny, III *et al.* 1996; Lewis *et al.* 1998; Mackenzie *et al.* 2003; Makela *et al.* 2000; Malerba *et al.* 1999; Neuhaus *et al.* 2005; Pirayesh *et al.* 2001; Rossi *et al.* 1993; Shiloni *et al.* 1993; Singer *et al.* 2003; Stoeckle *et al.* 2001; van Doorn *et al.* 1994; Wang *et al.* 1994; Youssef *et al.* 2002; Zornig *et al.* 1992) of people with RPSTS published since 1990, hospitals admitted between 2 and 42 patients for treatment per year on average. The difficulties associated with the treatment of this group of patients were a consistent theme. Patients tended to present with large tumours, (median size ranged from 10 to 18cm) which were predominantly high grade. Reports of 5 year overall survival varied between 19% and 63%. Between 40% and 96% of patients in each hospital received macroscopic surgical clearance of their tumour.

The rate of surgical resection with clear microscopic margins, where reported, was considerably lower.

Statistical meta-analysis of patient outcomes by institutional case volume was inappropriate because of important differences between the patient populations of the individual studies. Some case series, for example, included only people with localised primary tumours treated with curative intent. Due to the rarity of retroperitoneal sarcoma, case series even from large institutions often span decades to capture sufficient numbers for statistical analysis. It is difficult to interpret historical improvements and institutional differences in patient outcomes due to changes in patient management practices and technologies over this time.

Table 7 Are outcomes better for patients with suspected abdominal or pelvic STS treated in specialist sarcoma units than for those treated in non specialist units?

Abbreviations: CPY, average number of cases per year; DSS, disease specific survival; DFS, disease-free (local recurrence free) survival; MFH, malignant fibrous histiocytoma; MTS, median tumour size; OS, overall survival; POM, perioperative mortality; R0/R1, macroscopically clear resection; R0, microscopically clear resection; RPSTS, retroperitoneal soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
van Dalen *et al.* (2004)	To develop a post surgical classification system to allow comparison of outcomes for patients with RPSTS.	Case series.	Patients treated at a single tertiary referral centre (n=107). Patients treated elsewhere (n=124) were identified from population based records.	Overall 5 year survival. Completeness of surgical resection.	Overall 5 year survival: 55% in the tertiary centre and 43% in other centres (p=0.02). In a comparison of stage-specific 5 year survival, only class I patients (low grade, complete resection and no metastasis) had significantly better survival in the tertiary centre. Completeness of resection: Complete resection was more likely in patients treated at the tertiary centre than in those treated elsewhere, 84% vs. 67% (p = 0.02).		3+
van Dalen (2000)	To investigate the influence of surgical experience on survival in RPSTS.	Case series	Population based case series of 143 patients with retroperitoneal STS diagnosed between 1989 and 1994. Series included: 54 liposarcoma, 42 leiomyosarcoma and 10 MFH. 123 patients had surgical treatment and 20 patients did not. 52 (36%) patients were misdiagnosed preoperatively and originally treated for other assumed conditions.	Overall survival and completeness of tumour resection.	Surgical volume of hospital was dichotomised: =1 patient per year vs. <1 patient per year (on average). 35 patients were treated at 'high volume' (defined as at least 1 patient per year) hospitals and 108 treated else were. Overall survival: In a univariate analysis (log rank test) patients who were treated in a 'higher volume' hospital did not have a better prognosis (p=0.96). A correct pre-operative diagnosis was not associated with survival (p=0.69).	Author notes that one patient annually is probably not the correct cut-off point to consider a treating surgeon as experienced. Unclear how hospital volume related to surgeon volume in this study; different surgeons could have been operating from case to case. Not reported whether preoperative misdiagnosis was more likely in low volume centres.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
			NETHERLANDS				
					In a multivariate analysis (Cox regression) independent factors associated with improved survival were an R0/R1 resection, low malignancy grade and the absence of distant metastases. Hospital surgical volume was eliminated from the Cox regression as a prognostic factor (p>0.10). Radical resection: Extent of surgery was dichotomised: complete resection (R0/R1) vs. no complete resection (R2/no surgery). Treatment in a higher volume hospital was not related to completeness of resection in univariate analysis (p=0.26) but in a multivariate analysis it was an independent predictor of completeness of resection (p=0.0004). Fixation of tumour was the other predictor of completeness of surgery (p<0.0001). Author's conclusions: There was a higher chance of obtaining a radical resection in higher surgical volume hospitals, but the study did not find a better long-term outcome in these patients.	Event rate probably too low for the number of factors considered in the prognostic model.	

Table 7 (continued) Institutional case series

									Outcomes (figures are percentages)						
Study & level	***Institution & country***	***Years***	***n***	***CPY***	***Population***	***Stage at presentation***	***Tumour grade****	***MTS (cm)***	***R0/R1 rate***	***R0 rate***	***POM***	***5yr OS***	***10yr OS***	***5yr DFS***	***10yr DFS***	***Comments***
Bautista *et al.* (2000) 3	Kaiser Permanente Medical Centre, Los Angeles. USA	1985–1998	23	2	Patients with non-metastatic RPSTS.	96% had localised disease. 1 patient had sarcomatosis.	38% high 62% low	>15	91	91	0	26	13			Excess of low grade tumours. Low survival given complete resection rate. 2 patients (9%) died of post-operative chemotherapy complications
Catton *et al.* (1994) 3	Princess Margaret Hospital. CANADA	1975–1988	104	8	All RPSTS patients managed with surgery and radiotherapy.	71% primary disease, 19% primary recurrence, 10% metastases.	65% high 35% low	17	43	6		36	14	28	9	
Gilbeau *et al.* (2002) 3	Institut Bergonie Cancer Centre. FRANCE	1990–2000	45	5	New patients presenting to the institution with localised primary tumour. Therapy was combined surgery + RT.	100% localised primary disease.	76% high 24% low	18	58	38	4	60	40	40	20	

* Sarcomas reported as intermediate grade were counted as high grade.

									Outcomes (figures are percentages)							
Study & level	***Institution & country***	***Years***	***n***	***CPY***	***Population***	***Stage at presentation***	***Tumour grade****	***MTS (cm)***	***R0/R1 rate***	***R0 rate***	***POM***	***5yr OS***	***10yr OS***	***5yr DFS***	***10yr DFS***	***Comments***
Gronchi *et al.* (2004) 3	Instituto nazionale per lo studio e la cura dei tumori. ITALY	1982–2001	167	9	Patients treated with curative intent for non metastatic RPSTS.	85% localised disease, 15% lung metastases.	65% high 35% low	28 lipo 11 others	88		4	54	27	28	16	
Hassan *et al.* (2004) 3	Mayo Clinic. USA	1983–1995	97	12	Patients undergoing surgery for primary RPSTS.	88% localised disease, 12% distant metastases.	79% high 21% low		78		2	45	29			
Herman *et al.* (1999) 3	Marie-Sklodowska-Curie Memorial Institute of Oncology. POLAND	1965–1974	70	2	Patients with RPSTS treated at the institution.			Mean 18	67		4	39	29			27% of patients had no resection.
Ho *et al.* (1991) 3	Taichung Veterans Hospital. TAIWAN	1982–1990	16	2	Patients with primary RPSTS treated at the institution.	Not stated (all primary RPSTS).			56			19		13		5 year OS was 19% at most
Jenkins *et al.* (1996) 3	Royal Marsden Hospital (RMH). UK	1990–1995	119	24	All patients with RPSTS referred to the RMH. Paediatric patients & those with gynaecological tumours were excluded.		54% high 46% low	Mean 17.5	49		0	20				65 (55%) patients were operated on before referral to RMH. Survival was measured from time of presentation at the RMH.

Study & level	Institution & country	Years	n	CPY	Population	Stage at presentation	Tumour grade*	MTS (cm)	Outcomes (figures are percentages)							Comments
									R0/R1 rate	R0 rate	POM	5yr OS	10yr OS	5yr DFS	10yr DFS	
Karakousis *et al.* (1995) 3	Roswell Park Cancer Institute. USA	1977–1995	90	5	Patients with localized RPSTS.	All localised disease.	60% high 40% low		96		0	63	46	47		
Kilkenny, III *et al.* (1996) 3	University of Florida College of Medicine. USA	1970–1994	63	3	All primary cases of RPSTS undergoing resection.	90% localised disease, 10% metastatic.	54% high, 46% low.		78	63	0	48	37			
Lewis *et al.* (1999) 3	Memorial-Sloan Kettering Cancer-Centre. USA	1982–1994	500	42	Patients undergoing treatment for RPSTS at a single institution.	56% primary disease, 44% recurrent disease.	64% high 36% low		59	42	4	53	36			Survival analysis is for those with primary disease who underwent resection. OS is disease specific survival in this study.
Mackenzie *et al.* (2003) 3	Western Infirmary, Glasgow. UK	1990–2001	61	6	All patients with STS who were candidates for surgical resection.	54% primary disease, 36% recurrent, 10% metastatic.			74		3	62				Survival figures only include those with complete resection.
Makela *et al.* (2000) 3	University of Oulu. FINLAND	1977–1996	32	2	All patients with RPSTS diagnosed and treated at the institution (excluding GI tract STS).	6% had metastatic disease.		10–15	75	44	3	31	19			

									Outcomes (figures are percentages)							
Study & level	***Institution & country***	***Years***	***n***	***CPY***	***Population***	***Stage at presentation***	***Tumour grade****	***MTS (cm)***	***R0/R1 rate***	***R0 rate***	***POM***	***5yr OS***	***10yr OS***	***5yr DFS***	***10yr DFS***	***Comments***
Malerba *et al.* (1999) 3	Catholic University of the Sacred Heart, Rome. ITALY	1984–1995	42	4	All patients with RPSTS undergoing surgical exploration.		53% high 47% low	11–20	60	32	5	55		40		Survival data were only available for patients with radical resection.
Neuhaus *et al.* (2005) 3	Royal Marsden Hospital. UK	1990–2003	119	9	Patients with retroperitoneal liposarcoma.	61% primary surgery, 39% surgery for recurrence.	43% high 57% low	30	88		2	55	40	37	21	Figures relate to primary surgery only (72 patients) & were extracted from graphs.
Pirayesh *et al.* (2001) 3	Sarcoma centre, Royal University Hospital, Liverpool. UK	1990–2000	22	2	Patients undergoing surgery for RPSTS.	82% primary disease, 18% local or distant recurrence.	59% high 41% low	>10	41		9	44				Short follow-up.
Rossi *et al.* (1993) 3	Padova University. ITALY	1980–1989	25	3	Patients with primary RPSTS admitted to surgical oncology department.	80% localised disease, 20% metastatic.	72% high 28% low	15 (mean)	40		4	47	16			
Shiloni *et al.* (1993) 3	Hassadah University Hospital. ISRAEL	1968–1988	41	2	All referred cases with high grade RPSTS.		100% high	(>5)	56		2	44	34	17	10	

									Outcomes (figures are percentages)							
Study & level	***Institution & country***	***Years***	***n***	***CPY***	***Population***	***Stage at presentation***	***Tumour grade****	***MTS (cm)***	***R0/R1 rate***	***R0 rate***	***POM***	***5yr OS***	***10yr OS***	***5yr DFS***	***10yr DFS***	***Comments***
Singer *et al.* (1995) 3	Brigham & Women's Hospital and Dana Faber Cancer Institute. USA	1970–1994	83	3	All cases of RPSTS.	78% primary disease, 22% locally recurrent.	70% high 30% low	10				58	50			
Singer *et al.* (2003) 3	Memorial Sloan Kettering Cancer Centre. USA	1982–2001	177	9	Patients with primary RP liposarcoma.	100% primary disease.	39% high 61% low	26	81	44		60	40			OS is DSS, figures taken from graphs.
Stoeckle *et al.* (2001) 3	FNCLCC cancer registry data. FRANCE	1980–1994	165	NA	Patients with primary RPSTS.	12% had metastatic disease; their outcome data is not included in this table.	84% high 16% low	15	65			49		48		Outcome figures relate to patients with no metastases at presentation and complete excision.
(van Doorn *et al.* 1994) 3	Netherlands cancer institute. NETHERLANDS	1973–1990	34	2	Patients with potentially resectable RPSTS.	72% localised disease.	41% high 35% low		85		3	35		22		Survival data only reported for completely resected patients. 15% missing data for grade & stage.

									Outcomes (figures are percentages)							
Study & level	***Institution & country***	***Years***	***n***	***CPY***	***Population***	***Stage at presentation***	***Tumour grade****	***MTS (cm)***	***R0/R1 rate***	***R0 rate***	***POM***	***5yr OS***	***10yr OS***	***5yr DFS***	***10yr DFS***	***Comments***
Wang *et al.* (1994) 3	Shanghai Medical University. CHINA	1970–1989	19	2	Patients with their first local recurrence following complete resection of primary RPSTS.	All were locally recurrent. No metastases.	70% high 30% low	20	60		0	14				
Youssef *et al.* (2002) 3	B.A. Karmanos Cancer Institute, Wayne State University, Detroit. USA	1980–1998	60	3	Patients treated at the institution (combined surgery + RT).	75.5% localised primary, 23% metastatic, (1.5% unknown).	75% high 25% low		75	45	2	56	47	53	44	1 patient died of complications of therapy (therapy was surgery + RT).
Zornig *et al.* (1992) 3	University clinics of Hamburg. GERMANY	1970–1988	51	3	Patients treated with curative intent for non metastatic RPSTS.	43% localised disease, 57% regional and/or distant recurrence.	67% high 33% low	15	59	4		35	15			

Patients with STS requiring shared management

The questions

a) When is shared management, between site specific and specialist sarcoma MDTs, appropriate for people with STS?

b) What is the role for PET in the management of people with sarcoma?

Nature of the evidence

a) When is shared management, between site specific and specialist sarcoma MDTs, appropriate for patients with STS?

No studies specifically addressing shared management and outcomes in people with sarcoma were found. Expert opinion suggests that shared management would be appropriate for people with gynaecological, head and neck, skin, chest wall or CNS sarcomas; also for children with adult-type STS and for people with GIST.

Evidence about patterns of care and outcomes for people with gynaecological, head and neck, upper GI, and colorectal cancers, and for children and young adults with cancer is reviewed in the NICE improving outcomes service guidance series. This evidence was not reappraised for this review but is summarised below for reference.

b) What is the role for PET in the management of people with sarcoma?

Two systematic reviews of good quality considered the use of PET in people with, or suspected of having, sarcoma. One review covered PET for the detection, grading and therapy response of both study soft tissue and bone sarcomas (Bastiaannet *et al.* 2004) and the other considered PET for the detection and grading of STS only (Ioannidis & Lau 2003).

Sixteen observational studies of variable quality, not included in the above systematic reviews, were also appraised. The study populations were people diagnosed with (or suspected of): STS (Aoki *et al.* 2003; Cobben *et al.* 2004; Johnson *et al.* 2003; Kole *et al.* 1999); bone sarcoma (Aoki *et al.* 2001;

Bohuslavizki *et al.* 2000; Brenner *et al.* 2004; Franzius *et al.* 2002); musculoskeletal tumour (Watanabe *et al.* 2000) or GIST (Antoch *et al.* 2004; Choi *et al.* 2004; Gayed *et al.* 2004; Goerres *et al.* 2004; Jager *et al.* 2004; Stroobants *et al.* 2003). Most studies were retrospective observational studies, that were not well designed to evaluate the diagnostic utility of PET.

The use of PET for the detection of hepatic metastases from gastrointestinal cancers is considered in the assessment report accompanying NICE technology appraisal 86: Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours.

Two guidelines covered the use of PET in STS or bone sarcoma (American College of Radiology (ACR) 2002; Bourguet & Groupe de Travail 2003; O'Doherty *et al.* 2003). A strategic report by Intercollegiate Standing Committee on Nuclear Medicine considered the role of PET in sarcoma (O'Doherty *et al.* 2003), as did two review articles (Brenner *et al.* 2003; Israel-Mardirosian & Adler 2003).

Summary of the supporting evidence for the recommendations

a) When is shared management, between site specific and specialist sarcoma MDTs, appropriate for people with STS?

There is evidence throughout the NICE improving outcomes guidance series that management by an appropriate site specific specialist MDT is associated with improved patient outcomes. This is consistent with the recommendation that site (or age) specific MDTs should take primary responsibility for the management of people with sarcoma at certain anatomic sites.

STS arising in children

NICE guidance on *Improving Outcomes in Children and Young People with Cancer* recommends that surgery for non-rhabdomyosarcoma (adult type) STS, particularly in young people, should only be undertaken following review at a designated sarcoma MDT, although no evidence is offered in support of the recommendation.

The guidance recommends that children and young people with a rhabdomyosarcoma should be treated by the local paediatric MDT. In cases where the round cell tumour lump is unusual or poses particular problems, the paediatric surgeon should consult with the Sarcoma MDT. Evidence, from a retrospective UK case series (Stiller 1988), demonstrated that survival for children with Ewing's sarcoma, rhabdomyosarcoma or osteosarcoma was improved at paediatric oncology centres compared with non UKCCSG centres.

Uterine soft tissue sarcoma

Evidence for the optimal configuration of services for patients with gynaecological cancer is reviewed in the NHS Executive guidance Improving Outcomes in Gynaecological Cancers. Good quality observational and audit studies found that specialist gynaecological oncologists were more likely to provide appropriate surgery and adjuvant therapy and that patients managed by such surgeons had improved survival.

There was consistent evidence that patients with endometrial or cervical cancer treated in hospitals managing greater number of patients had better outcomes. Management by a multidisciplinary team was associated with improved survival in Scottish patients with ovarian cancer, although it was not possible to separate the effect from that of specialist care.

Head and neck soft tissue sarcoma

An expert position paper submitted to the GDG recommended that, while surgery should be undertaken by head and neck surgeons, people with STS of the head or neck should be discussed by both sarcoma and head and neck MDTs prior to definitive treatment.

The NICE guidance on Improving Outcomes in Head and Neck Cancer considers evidence for the specialist multidisciplinary management of people with cancer of the head or neck.

A study in the west of Scotland found that the outcomes of people with oral cancer managed by a specialist team were better than those treated in non-

specialist units. Further analysis suggested that the specialist unit was more likely to give effective, individually designed treatment. Similarly a study of treatment for thyroid cancer found that English patients treated by a multidisciplinary team of specialists were more likely to receive adequate treatment than those managed by other doctors. A large US study of surgical experience in thyroidectomy noted that greater experience was related to fewer complications and a shorter stay in hospital.

Sarcoma of the Skin

NICE guidance on Improving Outcomes in Skin Cancer recommends that there should be a close liaison between the SSMDT [specialist skin cancer MDT] and the STS MDT. It is appropriate for many cutaneous sarcomas to be considered by the SSMDT but some should also be discussed at the sarcoma MDT, especially those that penetrate the superficial fascia, or that require chemotherapy. No evidence was available to support this recommendation.

Gastrointestinal sarcoma

The NICE guidance on Improving Outcomes in Colorectal Cancers reviewed evidence from six systematic reviews and 33 observational studies regarding the effect of surgical specialisation and hospital volume on outcomes of people with colorectal cancers. There was consistent evidence to support the association between surgical specialisation, high case load and better outcomes for people with rectal cancer. There was limited evidence to support such an association in people with colon cancer.

Evidence for the relationship between specialist multidisciplinary treatment and survival is also reviewed in the NHS Executive Guidance on Improving Outcomes in Upper Gastro-intestinal Cancers. Direct evidence on the effectiveness of multidisciplinary teams was lacking but evidence from observational studies suggested that patients managed by such teams were more likely to get appropriate treatment. A consistent relationship between higher case load or specialisation and better outcomes in people with upper gastro-intestinal cancer was evident.

NICE technology appraisal 86: Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours recommends that the use of imatinib should be supervised by cancer specialists with experience in the management of people with unresectable or metastatic GISTs. The document does not consider whether this expertise is more likely to be found in a sarcoma or a gastrointestinal cancer MDT.

a) What is the role for PET in the management of sarcomas?

Two systematic reviews found insufficient evidence to support the routine use of FDG-PET in the diagnosis of suspected sarcoma. FDG-PET has the potential to discriminate between high grade sarcomas and low grade sarcomas or benign tumours, but may not offer adequate discrimination between low-grade sarcomas and benign tumours.

One of the systematic reviews of studies of bone and soft tissue sarcomas (Bastiaannet *et al.* 2004) concluded that while FDG-PET could discriminate between sarcomas and benign tumours and between low and high grade sarcomas, the quality of clinical studies to date was poor. Thus there was insufficient evidence to advocate the use FDG-PET in the standard treatment of sarcomas.

A second systematic review (Ioannidis & Lau 2003), limited to studies of people with STS, concluded that FDG-PET has very good discriminating ability in the evaluation of both primary and recurrent soft-tissue lesions. This review suggested that FDG-PET may be clinically helpful in tumour grading, but it may not always offer adequate discrimination between low-grade tumours and benign tumours. Both reviews emphasised the need for future research focusing on clinically relevant issues in diagnosis.

Detection of local recurrence

FDG-PET appears to have relatively high specificity in the diagnosis of local recurrence but has limited sensitivity. It may have a role in ruling in a diagnosis of local recurrence (Franzius *et al.* 2002; Ioannidis & Lau 2003; Johnson *et al.* 2003).

Detection of metastases

As an adjunct to CT, FDG-PET can improve the detection of pulmonary metastases in sarcoma. As a whole body imaging device FDG-PET may also detect distant recurrences in sites not shown on a chest CT (Antoch *et al.* 2004; Brenner *et al.* 2003; Johnson *et al.* 2003).

Occasionally PET will identify disseminated bone disease in Ewing's sarcoma that is missed on isotope bone scan and can be used to ensure that complex and dangerous surgery is not contra-indicated due to the presence of distant disease (Franzius *et al.* 2002).

Evidence for the use of FDG-PET for the detection of hepatic metastases from gastrointestinal cancers is considered in the assessment report accompanying NICE technology appraisal 86: Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. A meta-analysis of non-invasive imaging methods found FDG-PET to be more sensitive than CT, MRI and US methods.

Response to imatinib therapy in patients with GIST

Evidence from observational studies (Antoch *et al.* 2004; Choi *et al.* 2004; Gayed *et al.* 2004; Jager *et al.* 2004; Stroobants *et al.* 2003) suggests that FDG-PET is a sensitive indicator of early response to imatinib therapy, in people whose GISTs are measurable using FDG-PET.

Guiding tumour biopsy

FDG-PET may be useful in assessing tumour heterogeneity in order to guide a biopsy to areas of highest grade (Bohuslavizki *et al.* 2000; Bourguet & Groupe de Travail 2003; O'Doherty *et al.* 2003).

Table 8 What is the role of PET in the management of patients with sarcoma?

Abbreviations: ceCT, contrast enhanced computerized tomography; CT, computerized tomography; EORTC, European Organization for Research and Treatment of Cancer; FDG, 18F-fluorodeoxyglucose; FMT, Fluorine-18 labelled alpha-methyltyrosine; GIST, gastrointestinal stromal tumour; MRI, magnetic resonance imaging; PET, positron emission tomography; RCT, randomised controlled trials; STS, soft tissue sarcoma; SUV, standard uptake value; RECIST, response evaluation criteria in solid tumours;

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
American College of Radiology (ACR) (2002).		Guideline.			The guidelines do not make any recommendations for the use of FDG-PET in the follow up of bone and soft-tissue tumours due to limited evidence. They comment that the data so far are encouraging regarding FDG-PET and the detection of lung metastases and local recurrence, and that the issue will be revisited when more data become available. Authors' conclusions: MRI, CT, and PET are all needed to identify the extent of disease in follow up (data for PET are encouraging but still unproven). They admit this is a costly suggestion and that others have not yet advocated this extensive follow up protocol in a routine clinical setting.		4
Antoch *et al.* (2004)	To compare the value of PET, CT and dual-modality PET-CT for assessing GIST response to imatinib.	Case series and diagnostic study.	20 patients with GIST (verified histopathologically). GERMANY	Number of lesions detected, tumour response to therapy.	Dual modality PET-CT imaging was performed before initiation of imatinib therapy and at 1,3 and 6 months afterwards. PET images were read by 2 nuclear medicine physicians; CT images were read by 2 general radiologists; side-by-side and fused PET-CT images were read by both. The number of metastases detected in all patients was: 135 with PET, 249 with CT, 279 with side-by-side PET-CT and 282 with fused PET-CT.	Clinical follow up of 381±134 days served as the standard reference. This encompassed all available clinical data including the PET-CT imaging. Not clear how patients were selected for the study.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Tumour response was correctly characterised with PET-CT in 95%, 100% and 100% of patients at 1,3 and 6 months post treatment, compared with 85%, 100% and 100% for PET alone and 44%, 60% and 57% for CT alone.		
Aoki *et al.* (2001)	To compare the standardised uptake value (SUV) of 18F-FDG-PET at PET in benign vs. malignant bone lesions.	Case series and diagnostic study.	52 patients with primary bone lesions (19 malignant, 33 benign). JAPAN	SUV and tissue diagnosis of lesion.	Overall there was a significant difference in the SUV of benign and malignant tumours. No single cut-off SUV could be selected to distinguish between benign and malignant tumours. High FDG accumulation was seen in some benign lesions especially histiocytic or giant cell containing lesions. Authors' conclusions: FDG PET should be used for selected cases after careful evaluation of clinical and other radiologic findings.	SUV did not distinguish benign from malignant tumours. A number of different histologic sub-types were combined in the study. Standard reference was based on pathological examination of tissue.	3+
Aoki *et al.* (2003)	To evaluate the SUV of [(18)F]2-deoxy-2-fluoro- d-glucose at FDG-PET for preoperative differential diagnosis between benign and malignant soft tissue masses.	Case series.	One hundred and fourteen soft tissue masses (80 benign, 34 malignant) were examined by FDG-PET prior to tissue diagnosis. All patients were seen in a single institution between 1997 and 2000. JAPAN	SUV and tissue diagnosis of lesion.	There was a statistically significant difference in SUV between benign (1.80±1.42 [SD]) and malignant (4.20±3.16) soft tissue masses in total (P<0.0001). However, a considerable overlap in SUV was observed between many benign and malignant lesions. Liposarcomas (2.16±1.72) and synovial sarcomas (1.60±0.43) did not show significantly higher SUV than any benign lesions. Metastases (4.23±2.35) showed no statistically significant difference in SUV as compared with schwannomas (1.75±0.84), desmoids (2.77±1.32), sarcoidosis (3.62±1.53), or giant cell tumours of tendon sheath (GCT of TS; 5.06±1.63). Malignant fibrous histiocytomas (5.37±1.40) could not be differentiated from sarcoidosis or GCT of TS, based on the SUV.	Some of the tumour subgroups compared statistically contained only 3 lesions. Only lesions scheduled for resection or biopsy were included, possible bias towards higher grade lesions. A large accumulation of FDG can be observed in both benign and malignant histiocytic, fibroblastic, or neurogenic lesions. This could limit the usefulness of SUV in conventional FDG-PET in differentiating benign from malignant soft tissue masses.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Bastiaannet *et al.* (2004)	To assess the diagnostic value of FDG-PET in the detection, grading and therapy response of soft tissue and bone sarcomas.	Systematic review and meta-analysis of diagnostic studies.	29 studies n = 1258; 11 STS, 6 osteosarcoma and 12 mixed. Total number of patients in a study ranged from 5 – 202. Inclusion criteria: clinical studies, evaluating FDG-PET and sarcomas. Exclusion criteria: studies using other radio - pharmaceuticals case reports, reviews, editorials.	Detection, grading, evaluation of therapy response. 10 studies reported only on detection, 10 combined this with grading, 4 only studied grading and 5 of the 29 studies evaluated therapy response. 7 studies compared FDG-PET with another index test and most studies had histopathology as the reference standard.	17 studies provided sufficient data for the calculation of sensitivity and specificity for the detection of sarcomas. Pooled sensitivity: 0.91 (95% CI 0.89 – 0.93) Pooled specificity: 0.85 (95% CI 0.82 – 0.88) Pooled accuracy: 0.88 (95% CI 0.86 – 0.90) The difference between the mean Standard Uptake Value (SUV) in malignant and benign tumours for the studies concerning mixed and STS was statistically significant, as well as the difference in FDG uptake between low and high grade mixed sarcomas. Not enough studies to evaluate the therapy evaluation with FDG-PET. Authors' conclusions: Results indicate that in general FDG-PET has the potential discriminate between sarcomas and benign tumours and between sarcomas of low and high grade. The diagnostic implications of these results have to be investigated, especially the discrimination between benign tumours and low grade sarcomas. Based on this meta-analysis, however, there is no indication to use FDG-PET in the standard treatment of sarcomas.	PubMed, Embase and Cochrane searched (June 2002). Unclear if limited to English language. Study overlap (repeat publication) is not estimated; some authors have multiple appearances in the study list and bias is likely. No attempt to find grey literature – publication bias? Criteria for assessing methodological quality given and 3 reviewers performed reviews. Few studies with comparable outcome parameters. Some of the studies discussed combined both bone and soft tissue sarcomas. By using pooled sensitivity and specificity this study may have underestimated them. Could have included a summary receiver operating characteristic curve (SROC) to account for different test thresholds. Quality of studies was generally poor.	2+
Bohuslavizki *et al.* (2000)	To define the value of 18F-FDG- PET in clinical management of patients with osteosarcoma based on current treatment regimen.	Retrospective case series and diagnostic study.	18 patients (4 female, 14 male) aged from 14 to 63 years with primary osteosarcoma (n=6) or suspect for relapse of osteosarcoma (n=12). GERMANY	Accuracy of 18F-FDG PET vs. histologic (biopsy) diagnosis.	18F-FDG-PET clearly depicted primary osteosarcomas in 6/6 patients and a relapse of osteosarcoma in 2/2 patients. In the remaining 10 patients histology could not confirm a relapse of osteosarcoma. Authors' conclusions: 18F-FDG-PET had no significant impact in initial staging. Nevertheless, it might be helpful in	No patients with benign lesions were included.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					several clinical settings following neoadjuvant chemotherapy and surgical treatment of the primary tumour.		
Bourguet & Groupe de Travail (2003)	To define evidence based guidelines for the use of PET in bone and soft tissue sarcomas.	Evidence based guideline.	17 studies were reviewed.		STS: Review concludes that there is not sufficient data in the literature to define standards for the use of FDG-PET in STS. FDG-PET cannot be reliably used to determine the malignancy of a tumour. PET could be used to assess the heterogeneity of a tumour allowing a biopsy to be guided to areas of highest grade. PET may also have a role in surveillance for local tumour recurrence. Bone sarcoma: Review concludes that there is not sufficient data in the literature to define standards for the use of FDG-PET in bone sarcoma. Despite the small number of studies, PET may have a role in characterising the aggressiveness of a primary bone lesion.	French language, only the main conclusions translated. Guidelines formulated by the working group of the SOR but the makeup of this group is not clear from the paper.	4
Brenner *et al.* (2003)		Review.			Tumour grading: FDG-PET cannot differentiate benign from malignant lesions because of overlap in FDG-uptake (SUV). FDG-PET may be useful in guiding a biopsy to the higher grade areas of a heterogeneous tumour. Osteosarcoma staging and restaging: The sensitivity for FDG-PET is unsatisfactory for detecting lung and bone metastases. Therapy monitoring: FDG-PET seems to reliably predict tumour response in neoadjuvant therapy in osteosarcoma.		4

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Local recurrence: FDG-PET may be useful for differentiating tumour regrowth from fibrosis. In patients with metallic prostheses FDG-PET is likely to be superior to MRI for detection of local recurrences. Author is unable to draw definite conclusions regarding the indication for PET in osteosarcoma, mainly due to the limited amount of research evidence.		
Brenner *et al.* (2004)	To assess the potential of FDG PET for tumour grading in chondrosarcoma patients and to evaluate the role of standardized uptake value (SUV) as a parameter for prediction of patient outcome.	Case series.	31 patients with histologically proven chondrosarcoma who underwent PET imaging between 1995 and 2002. USA	The sensitivity and specificity of FDG-PET maximum SUV in the prediction of local and distant recurrence.	Chondrosarcomas were detectable in all patients. Tumour SUV was 3.38±1.61 for grade I (n=15), 5.44±3.06 for grade II (n=13), and 7.10±2.61 for grade III (n=3). Significant differences were found between patients with and without disease progression: SUV was 6.42±2.70 (n=10) in patients developing recurrent or metastatic disease compared with 3.74±2.22 in patients without relapse (P=0.015). Sensitivity, specificity, and positive and negative predictive values for a relapse base on tumour grade (II vs. III) were 90%, 67%, 56%, and 93%, respectively. Using a cut-off of 4 for SUV, sensitivity, specificity, and positive and negative predictive values for a relapse were 90%, 76%, 64%, and 94%, respectively. Combining tumour grade and SUV, these parameters improved to 90%, 95%, 90%, and 95%, respectively.	Maximum SUV combined with histologic grade was a better predictor of tumour recurrence than either measure in isolation. It is not clear how patients were selected for the study. In this study the sensitivity of FDG-PET SUV in predicting recurrence is equal to that of histological grade (at 90%). SUV has a marginally better specificity at 76% compared to 67% for histological grade.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Choi *et al.* (2004).	To compare changes in tumour density on CT with glucose metabolism and SUV on PET and to develop criteria for evaluation of tumour response using CT in patients treated with imatinib.	Case series.	36 patients with metastatic GIST (173 tumours), enrolled on a phase III clinical trial of imatinib at one institution 2000–2001. Age range was 28–86 years. Pre-treatment PET scans were available for 29 patients. USA	Overall tumour response (OTR), size and density on CT; tumour peak SUV on PET. Measures were taken before and 2 months after start of imatinib treatment.	Significant decreases were seen in tumour density (mean 12.3H [16%], p<0.01) and peak SUV (mean 3.43 [64.9%], p<0.01). No statistical association between changes in density and changes in peak SUV was found. Overall tumour response, evaluated subjectively from CT, correlated better with the degree of change on peak SUV than density alone. If tumours were evaluated using the RECIST criteria most (75%) would have been categorized as having stable disease, despite the fact that 70% of the patients reductions in peak SUV on PET of more than 60%. Authors' conclusion: FDG PET is sensitive and specific for evaluating tumour response but cannot be used in patients whose baseline FDG PET results are negative for tumours. The use of tumour size on CT (RECIST criteria) may underestimate tumour response to imatinib treatment.	Unclear which (if any) measure of tumour response was the gold standard.	3-
Cobben *et al.* (2004)	To investigate the feasibility of 18F-3'-fluoro-3'-deoxy-L-thymidine PET (FLT-PET) for the detection and grading of STS.	Case series, diagnostic study.	Nineteen patients with 20 STS of the extremities. All patients seen at a single institution between 2002 and 2003. NETHERLANDS	Standardized uptake values (SUVs) and tumour: non-tumour ratios (TNTs) were compared with histopathologic parameters using French and Japanese grading systems.	Mean SUV, maximal SUV, and TNT could differentiate between low-grade (grade 1; n = 6) STS and high-grade (grade 2 and 3; n = 14) STS according to the French grading system (P = 0.001). Mean SUV, max SUV, and TNT correlated with mitotic score, MIB-1 score, the French and Japanese grading system (r = 0.550–0.747).	Well conducted, but small, diagnostic study. Although statistical differences between groups were observed there was considerable overlap between the SUV for different tumour grades. The clinical utility of FLT-PET is not established by this study (i.e. sensitivity and specificity for a given threshold SUV).	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Franzius *et al.* (2002).	To assess the diagnostic ability of positron emission tomography using FDG-PET in the detection of recurrences from malignant primary bone tumours compared with conventional imaging.	Case series, diagnostic study.	41 FDG-PET examinations from 27 patients (6 osteosarcomas, 21 Ewing's sarcomas) were evaluated. Patients were seen over a 5.5 year period. GERMANY	The sensitivity, specificity and accuracy of FDG-PET and conventional imaging in the detection of recurrences.	In 25 examinations reference methods revealed 52 sites of recurrent disease (local n = 7; distant: osseous n = 22, pulmonary n = 13, soft tissue n = 10). On an examination-based analysis FDG-PET had a sensitivity of 0.96, a specificity of 0.81 and an accuracy of 0.90. Corresponding values for conventional imaging were 1.0, 0.56 and 0.82.	Conventional imaging techniques consisted of MRI of the primary tumour site, thoracic CT, and Tc-99m bone scintigraphy. The reference methods were the histopathologic analysis and/or the clinical and imaging follow-up. FDG-PET showed a small advantage in the detection of osseous and soft-tissue recurrences compared with conventional imaging. Thoracic CT was superior for the detection of pulmonary metastases. Authors suggest a multi-centred clinical trial is warranted.	3+
Gayed *et al.* (2004)	To compare the usefulness of 18F-FDG-PET and CT in the staging and evaluation of early response to imatinib therapy in GIST.	Case series, diagnostic study.	54 patients with surgically unresectable GIST. USA		FDG-PET and CT scans were repeated at 2 (49 patients), 4–6 (17 patients), and 12–14 months (18 patients) after initiation of imatinib therapy. For detection of recurrence and metastases the sensitivity and positive predictive values for CT were 93% and 100%; whereas these values for 18F-FDG PET were 86% and 98%. Repeat scans at 2 months after therapy showed agreement between 18F-FDG PET and CT scans in 71.4% of patients (57.1% having a good response to therapy and 14.3% lacking a response). Discrepant results between 18F-FDG PET and CT were recorded for 28.6% of the patients. (18)F-FDG PET predicted response to therapy earlier than did CT in 22.5% of patients during a longer follow up interval (4–16 months), whereas CT predicted lack of response to therapy earlier than (18)F-FDG PET in 4.1%. Authors' conclusion: These findings suggest that 18F-FDG PET is superior to CT in predicting early response to therapy in recurrent or metastatic GIST patients.	The standard reference was a combination of other imaging modalities, biopsy studies and follow up studies. It is not reported which patients received which investigations. Unclear how patients were initially selected. Cases were included in the study after demonstration of unresectable disease on CT scans. Could bias estimates of sensitivity in favour of CT.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Goerres *et al.* (2004)	To compare the prognostic usefulness of PET, contrast enhanced CT and dual PET-CT in patients with GIST.	Case series.	28 patients with CD117-positive GIST treated at a single institution. Age range 21–76 years All patients were treated with imatinib mesylate (starting dose either 400 or 800 mg/day). SWITZERLAND	Survival and disease progression.	Overall survival: Median survival for the group (from the start of imatinib treatment) was 44.5 months. Sensitivity: Poorly reported but at least 5 lesions missed by PET were identified by CT. 2 skeletal lesions missed by CT were identified by PET. Prognostic value of PET and CT: A post treatment PET scan (between 11 and 111 days after start of treatment) without pathological FDG accumulation was associated with better overall survival and longer time to progression than a scan with FDG avid areas (p=0.001 and p=0.002 respectively). In contrast CT findings were not suitable for prediction of overall survival or time to progression, only 2/28 patients had a follow up CT scan considered to be normal. Authors' conclusions: Both PET and PET-CT provide important prognostic information and have an impact on clinical decision making in GIST patients. PET-CT precisely delineates lesions and thus allows for the correct planning of surgical interventions.	Assessment of disease progression was based (at least partly) on imaging so agreement would be expected.	3-
Ioannidis & Lau (2003)	To assess the value of 18F-FDG-PET in the diagnosis and grading of STS.	Systematic review and meta-analysis of diagnostic studies.	15 studies with 441 soft-tissue lesions (227 malignant, 214 benign); Total number of patients in any given study ranged from 4–102. Inclusion criteria: n>3 with at least 1 STS, evaluating FDG-PET	Diagnostic and grading performance were evaluated for qualitative visualization; standard uptake value (SUV, cut-offs of 2.0 and 3.0); and metabolic rate of glucose (MRG, cut-off of 6.0 micro-	For diagnosis of malignant versus benign lesions, typical pairs of sensitivity and specificity estimates from the summary receiver operating characteristic curves were 92% and 73% for qualitative visualization; 87% and 79% for SUV 2.0; 70% and 87% for SUV 3.0; and 74% and 73% for MRG 6.0.	PubMed, and Embase (to Feb 2002) searched with no language restriction. Expert investigators were contacted for additional data and clarification. Many studies had low patient numbers. Study quality was not addressed. A variable amount of radiopharmaceutical was used across studies (148–407 MBq).	2+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
			STS diagnosis and grading.	mol/100g/min).	Diagnostic performance was similar for primary and recurrent lesions. By qualitative interpretation, 18F-FDG was positive in all intermediate or high-grade tumours (95% confidence interval [CI], 97.3%–100%), 74.4% (95% CI, 58.6%–85.9%) of low-grade tumours, and 39.3% (95% CI, 29.1%–50.3%) of benign lesions (including 11 of 12 inflammatory lesions). Using an SUV cut-off of 2.0, respective rates were 89.4% (95% CI, 79.4%–95.6%), 33.1% (95% CI, 15.6%–55.3%), and 19.1% (95% CI, 10.6%–30.5%). Limited data on comparisons with MRI and CT showed no differences against 18F-FDG PET in diagnosing recurrent and metastatic disease. Authors' conclusions 18F-FDG PET has very good discriminating ability in the evaluation of both primary and recurrent soft-tissue lesions. 18F-FDG PET may be helpful in tumour grading but offers inadequate discrimination between low grade tumours and benign lesions.	9 studies estimated SUV and 5 studies MRG. Histology was the reference standard, but many patients with benign looking lesions did not have histologic confirmation.	
Israel-Mardirosian & Adler (2003)	To outline the value of PET in the management of STS.	Review.	32 papers included.		Author's conclusion: At this time PET cannot replace tissue biopsy but rather complements the biopsy to better understand the biological behaviour of STS.		4
Jager *et al.* (2004).	To assess whether FDG PET is suitable for response evaluation of imatinib mesylate treatment.	Case series, diagnostic study.	16 patients with unresectable or metastasized: GIST (n=14) or leiomyosarcoma (n=2). All tumours were c-KIT positive (CD117 staining). NETHERLANDS	SUVs were compared with the overall response to treatment, based on clinical and radiological response.	FDG-PET was carried out a few days before and 1 week after start of treatment with imatinib. Overall response to treatment was considered to be present in 11 patients, absent in 4 and not evaluable in 1. PET 1 week after the start of imatinib mesylate appeared to correctly predict this response in	The reference standard was radiology and clinical follow up. It is unclear (but unlikely) whether the FDG-PET and conventional imaging were performed blind to each other. This could increase overall accuracy but makes difficult to ascertain the individual	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					14/15 patients (sensitivity 93%, using 25% reduction in SUV as cut-off). FDG uptake changes after 1 week of treatment were of greater magnitude than tumour volume changes on computed tomography at 8 weeks. Progression-free survival was significantly better in patients with a PET response (P = 0.002). Authors' conclusions: FDG-PET is useful in the evaluation of GIST treated with imatinib mesylate. It appears to separate treatment responders from non-responders and is helpful in follow up and predicting treatment outcome.	sensitivity and specificity of each procedure.	
Johnson *et al.* (2003)	To compare the sensitivity and specificity of FDG-PET, CT and MRI in the detection of local and distant recurrences in sarcoma.	Retrospective case series.	28 consecutive patients undergoing FDG-PET scans in a single institution between 1998 and 2002. USA	Sensitivity and specificity of PET, CT and MRI in the detection of recurrences.	28 patients underwent 33 PET scans, 29 CT scans and 8 MRI scans. FDG-PET detected all 25 cases of local and distant recurrences with 100% sensitivity. CT was able to detect 18 of the 22 possible cases of recurrent disease, whereas MRI was able to detect 5 of 7 cases of recurrent disease. Authors commented that PET was particularly useful in patients with extensive histories of surgery and radiation therapy; the setting in which CT and MRI have the lowest specificity and sensitivity.	The standard reference was surgical pathology in 7 cases and a combination of clinical follow up (at least 6 months) and radiology in the others. Patient population had moderate to high clinical suspicion for relapse. Likely to overestimated sensitivity of the diagnostic tests in the general STS population. Small study, few patients had MRI scans.	3-
Kole *et al.* (1999).	To investigate the relationship of PET using fluorodeoxyglucose (FDG) or L-[1-11C]-tyrosine (TYR) with histopathologic	Case series, diagnostic study.	55 patients with a lesion suspected to be a malignant soft- tissue tumour. All tumours were larger than 2cm diameter. NETHERLANDS	Metabolic rate of glucose consumption (MRG) and protein synthesis rate (PSR). Histologic parameters: tumour grade, mitotic rate, proliferation and	9/55 (16%) tumours were benign. MRG correlated with tumour grade (r = 0.71) and mitotic rate (r = 0.68) but not with proliferation or necrosis. In 28 patients, a second PET study was performed after therapy. After therapy, there was no longer a correlation with mitotic rate. PSR	All patients were biopsied following PET to obtain a definite diagnosis.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
	findings in soft-tissue tumours, before and after therapy.			necrosis.	correlated with tumour grade (r = 0.53), mitotic rate (r = 0.73) and proliferation (r = 0.66). After therapy, correlation with mitosis and proliferation had improved, and a negative correlation was found between PSR and necrosis (r = -0.74). Authors' conclusions: These results validate both FDG and TYR to give an in vivo indication of histologic tumour parameters. However, FDG gives a better indication of tumour grade, whereas TYR is more accurate in predicting mitotic rate and proliferation, especially after therapy. FDG may therefore not be the most suited tracer for monitoring therapy. TYR might be more appropriate for that purpose.		
O'Doherty *et al.* (2003)	To outline the potential value andpractical implications of the development of a PET service.	Guidelines			The strength of evidence for recommendations was classified as: A. Randomised controlled clinical trials, meta-analyses, systematic reviews. B. Robust experimental or observational studies. C. Other evidence where the advice relies on expert opinion and has the endorsement of respected authorities. Indications for PET scanning in musculoskeletal tumours: 1. Soft tissue primary mass assessment to distinguish high grade malignancy from low or benign disease. (B) 2. Staging of primary soft tissue malignancy to assess non-skeletal metastases. (B) 3. Assessment of recurrent abnormalities in operative sites. (B) 4. Assessment of osteogenic sarcomas for metastatic disease. (C)		4

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					5. Follow up to detect recurrence or metastases. (B) Not indicated routinely (but may be helpful): 1. Image registration of the primary mass to identify optimum biopsy site. (C)		
Stroobants *et al.* (2003).	To evaluate if FDG-PET can be used for the early evaluation of response to imatinib mesylate treatment in STS.	Case series, diagnostic study.	24 patients (19 GIST, 5 other STS). GISTS were c-kit positive (CD117 staining). BELGIUM	Response of the tumour to treatment according to: CT, patient symptoms, and PET. Progression free survival.	3/24 patients were excluded because their tumours were not FDG avid, leaving 21 patients for further analysis. Lesions were scanned by CT 4 and 8 weeks after start of treatment and every 8 weeks thereafter. PET imaging was performed before treatment; at 8 and 28 days after start of treatment and every 8 weeks thereafter. PET response (using EORTC guideline criteria) was observed in 13 GISTs (11 Complete Responders, 2 partial responders. Subsequent CT response according to Evaluation Criteria in Solid Tumours (RECIST) was observed in 10 of these patients after a median follow up of 8 weeks. Stable or progressive disease was observed on PET in 8 patients and none of them achieved a response on CT. PET response was also associated with a longer progression-free survival (92% versus 12% at 1 year, P=0.00107).	It is unclear (but unlikely) that the FDG-PET and conventional imaging were done blind to each other. This could increase overall accuracy but makes difficult to ascertain the individual sensitivity and specificity of each procedure.	3+
Watanabe *et al.* (2000)	To compare Fluorine-18 labelled alpha-methyl tyrosine (FMT) with FDG for the evaluation of musculoskeletal tumours.	Case series, diagnostic study.	75 patients having surgery for bone tumour (11 malignant, 16 benign) or soft tissue tumour (11 malignant, 37 benign) between 1998 and 1999. JAPAN	SUV for both FDG and FMT. The diagnostic sensitivity and specificity of FDG-PET and FMT-PET.	A significant correlation between FMT and FDG SUVs was found for all lesions (r=0.769, P<0.0001), and mean values for malignant tumours were significantly higher than those for benign lesions in both FMT- and FDG-PET. The diagnostic sensitivities and specificities for malignancy were 72.7% and 84.9%, respectively, using FMT with a cut-off SUV of 1.2, and 72.7% and 66.0%, respectively, using FDG with a cut-off SUV of 1.9. The resultant accuracy with FMT was 81.3%,	Final diagnosis was established using material taken at biopsy, surgical excision or autopsy for all patients.PET findings were also compared with CT and MRI images and results of pathological diagnosis. Possible bias.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					higher than that for FDG (68.0%), and the difference with respect to specificity was significant (chi^2=5.0625, P<0.05). While a significant correlation was found between malignant tumour grade and SUV with both FMT- (rho=0.656) and FDG-PET (rho=0.815), only the latter demonstrated significant differences among grades I, II and III. Authors' conclusions.: FMT and FDG for PET appear equally effective at detecting musculoskeletal tumours. In evaluating musculoskeletal tumours, FMT may be superior to FDG in the differentiation between benign and malignant tumours, while FDG may be the better choice for non-invasive malignancy grading.		

Treatment support staff

The questions

a) Is there any evidence to support the role of a key worker for people with sarcoma?

b) Do limb prostheses, as currently prescribed, suit patients' needs? (as measured by outcomes including function, quality of life and complications)

c) Are current limb fitting services providing an adequate service?

d) Does specialist rehabilitation (physiotherapy and occupational therapy) improve outcomes for people with sarcoma?

Nature of the evidence

a) Is there any evidence to support the role of a key worker for people with sarcoma?

No evidence about key workers for people with sarcoma was identified. Evidence about key workers for people with cancer is reviewed in the NICE guidance on *Improving Supportive and Palliative Care in Adults with Cancer*. This evidence was not reappraised for this review.

b) Do limb prostheses, as currently prescribed, suit patients' needs?

Five of the studies identified used a cross sectional survey design. One of these was of very high quality, one of good quality and three of poor quality. Eleven papers were based on surveys of patients drawn from the records of single institutions (case series). One of these studies was of good quality and the remaining ten were of poor quality.

All studies included users of prosthetic limbs in general and not exclusively people with cancer. The majority had lost their limb to trauma (in the case of upper limb amputations) or peripheral vascular disease (in the case of lower limb amputations).

Study samples included upper limb prosthesis users: (Datta *et al.* 2004; Davidson 2002; Dudkiewicz *et al.* 2004; Gaine *et al.* 1997; Kejlaa 1993; Routhier 2001);

lower limb prosthesis users: (Evans *et al.* 2003; Legro *et al.* 1999; Legro *et al.* 2001; Murray & Fox 2002) and upper or lower limb prosthesis users (Audit Commission 2000; Audit Commission 2002; Fisher & Hanspal 1998; Information and Statistics Division NHSScotland 2004; Pezzin *et al.* 2004; Smith *et al.* 1995).

The studies used (often *ad hoc*) questionnaire measures of prosthetic use and satisfaction. This raised questions of validity and made it difficult to compare individual studies. The proportion of the time spent using the prosthesis was employed as a surrogate measure of prosthetic usefulness and satisfaction. No study measured this directly, however; instead relying on patients' reports of their daily prosthesis use.

c) Are current limb fitting services providing an adequate service?

See previous section for the characteristics of the included studies.

d) Does specialist rehabilitation (physiotherapy and occupational therapy) improve outcomes for sarcoma patients?

Sarcoma-specific evidence was limited to unsystematic reviews and case reports of the rehabilitation process. No studies of the effectiveness of rehabilitation for people with sarcoma, or of specialist sarcoma physiotherapists, were found.

Two review papers (Gudas 2000; Parsons & Davies 2004) discussed the role of the physiotherapist in the rehabilitation of people with sarcoma. An observational case series (Frieden *et al.* 1993) and a case report (Heath 1999) described rehabilitation needs following limb sparing surgery for osteosarcoma or Ewing's sarcoma. Other reviews discussed the rehabilitation of children with sarcoma from the surgeon's (Pritchard 1981) and psychiatrist's (Griffith 1981) viewpoints. A cross sectional study (Mankin *et al.* 2004) surveyed patients about the long term effects of connective tissue cancer treatment on physical function.

Summary of the supporting evidence for the recommendations

a) Is there any evidence to support the role of a key worker for patients with sarcoma?

Although no studies specific to people with sarcoma were found, extrapolation from the evidence presented in the NICE guidance on *Improving Supportive and*

Palliative Care in Adults with Cancer supports the recommendation for key workers for people with sarcoma.

b) Do limb prostheses, as currently prescribed, suit patients' needs?

A significant proportion of limb prosthetic users are not satisfied with their prosthesis, suggesting that the prosthesis do not meet the needs of these people.

Studies reported the proportion of upper limb prosthetic users who were satisfied with various aspects of their prosthesis: usefulness 72% (Datta *et al.* 2004), comfort 66% (Davidson 2002) and appearance 77% (Datta *et al.* 2004). Overall satisfaction was rated as 55% (Dudkiewicz *et al.* 2004) 60% (Routhier 2001) and 69% (Davidson 2002).

Satisfaction was somewhat better amongst lower limb prosthetic users (in studies combining both upper and lower limb prostheses): usefulness 84% (Smith *et al.* 1995), comfort 74% (Smith *et al.* 1995), appearance 80% (Pezzin *et al.* 2004), weight 77% (Pezzin *et al.* 2004), socket fit 76% (Pezzin *et al.* 2004) and overall satisfaction 79% (Pezzin *et al.* 2004).

c) Are current limb fitting services providing an adequate service?

It is important to establish to what extent patient dissatisfaction is due to the inherent functional and cosmetic limitations of prosthetics and to what degree due to the deficiencies of limb fitting services. The evidence suggested at least some inadequacies in limb fitting services.

The Audit commission report in 2000 identified user concerns with aspects of the prosthetics service in the UK, especially with regard to the information provided to patients. The same report also found that approximately 25% of people fitted with prosthetic limbs found them unusable for reasons of discomfort, pain, poor fit and appearance.

In an update to the original report some improvements and examples of innovative practice were noted (Audit Commission 2002) but patients were not surveyed.

In a large US study (Pezzin *et al.* 2004) 75% of patients were (at least) satisfied with the technical skills, information giving and interpersonal manner of their prosthetist.

Delay in limb fitting of more than 8 weeks (Pezzin *et al.* 2004) (or 12 weeks (Gaine *et al.* 1997)) is associated with reduced prosthetic use and lower satisfaction. The UK National Amputee Statistical Database (Information and Statistics Division NHS Scotland 2004) reports the time interval from amputation to referral to prosthetics services as 2 weeks or less for 40% of patients and 16 weeks or less for 84% of patients. The time taken to supply the definitive prosthesis is not reported. Case mix is not considered in these studies but could be an important consideration, for example adjuvant therapy may complicate limb fitting in people with cancer.

d) Does specialist rehabilitation (physiotherapy and occupational therapy) improve outcomes for sarcoma patients?

There was limited evidence in support of the recommendation that a specialist sarcoma physiotherapist should be included as a member of the extended sarcoma MDT.

Two review papers stressed the importance of an experienced physiotherapist, trained in the post-treatment support of people with sarcoma, in helping people attain the best possible function (Gudas 2000; Parsons & Davies 2004).

The case series of Freiden and co-workers (Frieden *et al.* 1993) stated that the function of the patient's affected limb following surgery was related to adherence to a physiotherapy program, but without evidence. Another case report (Heath 1999) discussed the usefulness of a written plan during the rehabilitation of a young patient with Ewing's sarcoma. Other review papers stressed the importance of a structured rehabilitation programme for children with sarcoma who undergo amputation (Griffith 1981; Pritchard 1981). Observational (Frieden *et al.* 1993) and cross sectional (Mankin *et al.* 2004) evidence supports the need for rehabilitation in people with sarcoma.

Table 9.a Do limb prostheses, as currently prescribed, suit patients' needs? Are current limb fitting services providing an adequate service?

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HRQL, health related quality of life; SD, standard deviation.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Pezzin *et al.* (2004)	To examine the use and satisfaction with prosthetic devices and fitting services.	Cross sectional.	935 amputees, aged 18–84 years, identified at random from the Amputee Coalition of America registry. Aetiology was: dysvascular in 354 patients, trauma in 362 and cancer in 219. Patients with congenital limb deficiency were excluded. USA	Use and satisfaction with prosthetic devices and services (assessed via telephone interview).	Use of prosthesis: Most of those surveyed used a prosthesis (95%) and the average usage was 71 hours per week (SD 41 hours). Satisfaction with prosthesis: • 76% were satisfied with the overall performance of their prosthesis • 76% with the socket fit • 80% with the appearance • 77% with the weight. Multivariate analysis indicated that a delay in prosthesis fitting of >60 days was associated both with reduced use and satisfaction ($p<0.05$). Satisfaction with prosthetic services: More than 75% of patients were satisfied (or very satisfied) with the technical skills, information giving and interpersonal manner of their prosthestist. No significant differences were observed between prosthesis use and satisfaction of groups based on amputation level or aetiology. Efforts should be directed at minimising the interval from surgery to first prosthesis fitting and at improving communication between patients and prosthetists.	Study included mostly lower limb amputees (79%). Authors suggest that members of the ACA registry are a self-selected group and likely to be younger than the general population of amputees. Delay in limb fitting may be for clinical reasons independently associated with outcomes. Adjustment should be made for case mix in analysis.	3++

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Smith *et al.* (1995)	To develop a patient satisfaction system for disablement services centres and to report on how the initial findings have been used to improve the quality of service.	Case series.	Audit conducted in 1991 at 3 disablement services centres: Birmingham, Oxford and Cambridge. 1103 amputees were included. UK	Patient satisfaction scores for the components of the limb-fitting service.	Satisfaction was rated using a 4 point ordinal scale to derive a satisfaction score for each component of the limb fitting service. Scores ranged from 1.0 (very satisfied) to 0.25 (very dissatisfied). User satisfaction was high (>0.80) for the surroundings, layout, booking of appointments, waiting facilities and staff attitudes. Aspects scoring lower (<0.80) were wait in fitting room, information, counselling services, limb comfort, and number of alterations required to fit the limb properly. The Birmingham centre was re-audited in 1992 and an increase in patient satisfaction was noted in all areas ($p<0.05$) apart from limb usefulness. Authors' conclusions: The results suggest that the questionnaire enabled users' views to be fed back to staff and prompted improvement in the limb fitting service.	Audit was conducted in 1991 immediately after the disablement services authority was disbanded and the prosthetics service transferred to the NHS. Stated aim of the study was to develop a tool to measure satisfaction, but no validation was performed.	3+
Audit Commission (2002)	To document progress in equipment services following the original "Fully Equipped" report and identify what further action needs to be taken..	Observational study.		Progress on the recommendations of the original report (Audit Commission, 2000).	Authors conclusions: The allocation of a named prosthetist to each patient is generally accepted as good practice, although users stress the quality of the outcome is most important. Variability in the reporting of product failures to the Medical Devices Agency was observed. For provision of second limbs - judgement needs to be made on the basis of individual need.		3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Audit Commission (2000)	To report on the provision of some forms of equipment to older or disabled people by the NHS or social services in England and Wales.	Observational study.	2300 users of the prosthetics service who responded to a survey in 1999. Response rate was 64%. UK	User concerns with aspects of the prosthetic service. Reasons for not using artificial limbs.	User satisfaction: • 55% were not given information about voluntary organisations dealing with limb loss • 42% were not given information about social security benefits • 40% were given no written information. Other concerns included lack of information about: the limb fitting service (37%), new limbs and coverings (28%), treatment (22%) and care of prosthesis (21%). Approximately 25% of users discontinued the use of their prosthesis for the following reasons: Too uncomfortable (29%), too painful (25%), too heavy (18%), doesn't fit (12%), cannot wear with come clothes (11%) and doesn't look good (5%). Authors' conclusions: Trusts should allocate a named prosthetist for each patient. Product failures should be reported to the Medical Device Agency. Once an adequate repair service is established the provision of a second limb for adults should be limited to the provision of specialist or sports limbs. Access to counselling should also be provided.	No information provided about the characteristics of the study sample.	3-
Information and Statistics Division NHS Scotland (2004)	To summarise incident cases referred to UK prosthetics services.	Case series.	All new referrals recorded in the National Amputee Statistical Database (NASDAB) from April 2002 to April 2003. Data collected by 44 amputee care centres. UK	Incidence of upper and lower limb amputation. Time interval between amputation and referral to prosthetics centre.	Upper limb amputations: 26/301 (9%) were due to neoplasia, of which 19/301 (6%) were recorded as due to malignant primary tumours. Lower limb amputations: 140/5264 (3%) were due to neoplasia of which 109/5264 (2%) were recorded as due to malignant primary tumours.	Data on prosthetics not supplied.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Time interval from amputation to referral: 2 weeks or less for 40%, and 16 weeks or less for 84% of patients. Authors' conclusions: Lower limb amputations accounted for 92% of all amputations, upper limb for 5% and congenital deficiency for 3%. The most common cause of upper limb amputation remains trauma at 64%. In lower limb amputation, dysvacularity is the most common cause (75% of cases). 40% of all new referrals to prosthetics service centres were referred within 2 weeks of amputation.		
Evans *et al.* (2003)	To review the type of follow up received by amputees and its influence on their mobility and functional status.	Case series.	166 patients with primary lower limb amputation. Reasons for amputation were: peripheral vascular disease 77%, trauma 10%, infection 6%, carcinoma 1%, and other 6%. Multi centre study involving 12 acute hospitals and 2 limb-fitting centres. UK	Mobility status (on discharge from acute phase and 6 or more months later), amputee satisfaction and type of follow up received.	Mobility status (at discharge from acute phase vs. 6 months later): In 12 patients mobility status had decreased, in 34 patients mobility was unchanged and in 18 patients mobility improved. Follow up The limb-fitting centres followed the majority of patients (83%). Patients' satisfaction was not measured systematically but comments analysed thematically. Patients appeared generally happy with their initial rehabilitation but expressed concerns over lack of support and rehabilitation in subsequent stages. Authors' conclusions: Rehabilitation received by the amputees bore little resemblance to that planned at discharge. The planned programme was not carried through to the intermediate care stage and might not allow amputees to reach their optimal functional level.	Discrepancy between sample size quoted in text and in figures in table 1. Post acute phase and 6 month assessments done by different investigators, possible systematic bias. Data not analysed statistically.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Davidson (2002)	To investigate prosthesis wearing time and satisfaction levels in upper limb amputees.	Case series.	63 upper limb amputees and 7 limb deficient persons recruited from multiple centres. Loss of limb was due to trauma in 49/70 (70%) of cases, and malignancy, vascular disease or congenital absence in the remaining cases. AUSTRALIA	Satisfaction with prosthesis, satisfaction with functional activities and prosthesis wearing time.	Prosthetic wearing time: For each of the tasks identified there appeared to be 2 sub groups, one tended to wear their prosthesis most or all of the time, the other rarely wore their prosthesis. The second group predominated for most tasks. Satisfaction with functional activities: • 12% very satisfied • 14% quite satisfied • 52% OK • 14% quite unsatisfied • 8% very unsatisfied. Satisfaction with prosthesis: • 10% very satisfied • 15% quite satisfied • 44% OK • 16% quite unsatisfied • 16% very unsatisfied. Prosthesis wearing time was not associated with functional ability satisfaction (r=0.11) but appeared associated with prosthesis satisfaction (r=0.66). Author's conclusions: An increase in prosthesis wearing may increase an amputee's functional ability for specific tasks and activities even if it does not increase their level of satisfaction with their functional ability.	Questionnaires distributed via clinics and amputee associations. Selection bias in favour of prosthesis users. Quality of data analysis generally poor; mean used inappropriately to summarise ordinal data.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Kejlaa (1993)	To evaluate satisfaction with prostheses and estimate whether functional levels were related to prosthesis use.	Case series.	66 upper limb amputees. Loss of limb was due to trauma in 43/66 (65%) cases, congenital 10/66 (15%), vascular disease 4/66 (6%), tumour 3/66 (5%), and other 9%. Patients were identified from 1 county's hospital and limb-fitting centre records 1900–1987. DENMARK	Prosthesis wearing time, problems with the prosthesis and problems with functional ability.	Time since amputation: mean 20.6 years, range 0–63 years. 3 prosthesis types were used: a body powered mechanical system (BP), a myo-electric system (MYO) and a passive system (PAS). Prosthesis wearing time of more than 8 hours per day: • BP: 20/25 (80%) • MYO: 6/7 (86%) • PAS: 11/16 (69%) Problems with prosthesis: Active prosthesis (BP & MYO) had the highest number of problems. Most were concerned with the socket, and for BP with the suspension and control system. Problems with activities of daily life: Active prosthesis users had fewer problems than the other groups. Author's conclusions: Active fitting is a worthy effort. In daily living the active users have a superior performance over the passive and non-users.	No statistical analysis of data.	3-
Gaine *et al.* (1997)	To assess traumatic amputees in terms of their loss and success of prosthetic use compared with other amputees.	Case series.	55 upper limb amputees: 23 traumatic and 32 congenital. Patients with amputations following cancer were excluded. Patients were identified through a single prosthetic clinic. UK	Prosthesis wearing time and satisfaction with prosthesis.	Mean daily prosthetic wearing time: • Traumatic amputees: 6 hours • Congenitally limb deficient 9.3 hours. Overall rating of satisfaction with prosthesis: • Traumatic amputees: fair • Congenitally limb deficient: good. None of the traumatic amputees fitted after 12	The congenitally limb deficient group were younger and likely to have been using a prosthesis since childhood. No statistical analysis of data. Authors admit the comparison of traumatic and congenital amputees is of limited value.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					weeks returned to gainful employment Authors' conclusions: Early prosthetic fitting, rehabilitation and counselling are advocated in order to achieve an optimum prosthetic benefit for the patient.		
Routhier (2001)	To investigate the satisfaction level of young users of upper limb myoelectric prostheses.	Case series and unsystematic review.	10 children fitted with an upper limb myoelectric prosthesis between 1990 and 1999 in one region.	Prosthesis usage time and desirable features of prosthesis.	Prosthesis usage: 2/10 (20%) of the children were fulltime users (used the prosthesis for > 6 hours per day). 30% of children did not use their prosthesis. Satisfaction with prosthesis: 6 patients were very satisfied, 3 somewhat satisfied or rather unsatisfied and 1 was not satisfied. Desirable features of prosthesis identified through questionnaire: weight, comfort, freedom, installation, effectiveness, technical support, appearance, flexibility, simplicity of use and training. Authors conclusions: The dropout rate seems high compared with that of other studies. The provision of a multidisciplinary team and structured training and follow up is suggested to improve limb-fitting results.	Very small sample size. No statistical analysis of data.	3-
Murray & Fox (2002)	To examine the relationship between lower limb prosthesis satisfaction and body image.	Cross sectional.	46 putative lower limb amputees were recruited though postings to internet discussion groups. Reported causes of limb loss were 16 trauma, 16	3 questionnaires were used: Trinity amputation and prosthesis experience (TAPES), the amputee body image scale (ABIS) and	Body image disturbance was negatively correlated with prosthesis satisfaction (r=-0.52, p<0.01). Prosthesis use was positively correlated with	Patients were all internet users, selection bias? There was therefore no way to assess the quality of the data (e.g. that the respondents were actually prosthetic users). Sub group analyses were performed on	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
			cancer, 3 congenital, 2 peripheral vascular disease and 1 diabetes.	the McGill pain questionnaire (MPQ). Time of use of prosthesis (reported by patients).	prosthesis satisfaction (r=-0.39, p<0.01). The sub-components of prosthesis satisfaction (functional, aesthetic and weight satisfaction) were all similarly correlated with body image disturbance. Authors' conclusions: The present research is instructive of the close relationship between body image and prosthesis satisfaction in lower limb prosthesis users. These findings have implications for targeted service provision in prosthetic rehabilitation.	an already small sample. Unclear what the benefit of measuring body image in amputees might be.	
Dudkiewicz *et al.* (2004)	To investigate factors predicting successful prosthetic rehabilitation of upper limb amputees.	Case series, retrospective.	42 patients who had undergone an upper limb amputation. Aetiology was trauma (n=26), congenital absence (n=12), infection (n=2), tumour (n=1) and vascular (n=1). ISRAEL	Modified upper limb amputee's questionnaire, pain questionnaire, and functional assessment of prosthetic usage.	23/42 (55%) of patients were satisfied with their prosthesis. 30/42 (71%) of patients reported problems with prosthesis usage (weight of the prosthesis, irritation of the harness and excess sweating). Daily use of prosthesis types: Cosmetic type (n=31): 17 (55%) used it intermittently, 5 (16%) used it temporarily and 9 (29%) discontinued their use. Body powered prosthesis (n=10): 4 permanently, 3 intermittently and 3 discontinued their use.	Above-elbow, trans-elbow, below-elbow and trans-wrist amputees all included in study (but have different functional requirements from a prosthesis). Study does not identify any prognostic factors for successful prosthesis use.	3-
Legro *et al.* (1999).	To report prosthesis related issues of importance identified by lower limb amputees.	Case series.	92 lower limb amputees identified from the records of 2 institutions. Predominantly male sample (86%) with transtibial amputation (63%). USA	Prosthesis evaluation questionnaire and the standard-form-36 (a health status questionnaire).	Patients rated the fit of the prosthesis, ability to walk with the prosthesis, avoidance of blisters, sores or rashes as the most important factors associated with use of a prosthesis. Four themes of interest were identified from open ended questions about life with a prosthesis: the fit of the socket, mechanical functioning, physical	Patients were recruited from a regional trauma centre and veteran's hospital. Sample biased towards males with amputation due to trauma.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					qualities, and adaptation with support from others. Author's conclusions: Future research is recommended to adjust aspects of the fit of the prosthesis with the residual limb. Implementing periodic check-up visits could uncover problems and eliminate unnecessary suffering.		
Legro *et al.* (2001).	To describe the self-reported recreational activities important to persons living with a lower limb prosthesis.	Case series.	92 lower limb amputees identified from the records of 2 institutions. Predominantly male sample (86%) with transtibial amputation. Same sample as Legro et al (1999). USA	Preferred recreational activities of lower limb amputees. Ability to perform preferred recreational activities with and without the limb prosthesis.	Activities were rated as high, moderate or low energy, or sedentary by the authors. In the group of patients younger than 60 years, at least 69% of preferred activities were moderate or high energy level activities. In patients 60 years or older, at least 38% of activities were moderate or high energy. The average importance to the patient of their favourite activity was rated 87/100. On average patients rated their ability to do this activity as 67/100 with their prosthesis and 30/100 without their prosthesis. Author's conclusions: The wide variety of activities preferred by amputees with lower limb prostheses suggests to providers that it is wise to discuss patients' preferred recreational activities in order to facilitate optimal prosthetic adaptation.	Preference and ability were recorded using a visual analogue scale. Patients were recruited from a regional trauma centre and veteran's hospital. Sample biased towards males with amputation due to trauma, who may be more likely to prefer certain activities.	3-
Fisher & Hanspal (1998)	To establish whether dissatisfaction with the artificial limb or body	Case series.	188 patients, aged 40–88 years and at least 1 year post amputation, were recruited from a prosthetic clinic. Cause of amputation	Patients' attitudes to their prosthesis, HADS score, body image and mobility.	There was no correlation between the measure of attitudes to prosthesis and any of the other study measures.	Amputees who had discontinued the use of their prosthesis and stopped attending the clinic were not considered. This could bias towards a favourable impression of	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
	image relate to achieved mobility in lower limb prosthesis users.		was vascular disease and diabetes in 40%, trauma in 35%, infection in 8%, congenital in 8%, neoplasm in 5% and other in 4% of patients. UK		The body image dissatisfaction measure was positively correlated with HADS anxiety (r=0.56, p<0.01) and depression (r=0.39, p<0.05) measures. Mobility was negatively correlated with age (r = -0.41, p<0.05), but none of the other measures. Authors' conclusions: These results showed patients were moderately satisfied with their artificial limb, had little experience of body image disruption or distress and there was no relationship between these variables and mobility.	patient satisfaction. Body image and mobility were assessed in established amputees, it would be impossible to establish any cause and effect using this study design.	
Datta *et al.* (2004).	To investigate the functional outcome of patients with proximal upper limb deficiency.	Case series.	Patients were selected from the records of a sub-regional prosthetic and rehabilitation centre. 60/92 patients returned questionnaires. Aetiology was: trauma 71%, congenital 10% and other 19%. UK	Prosthetic usage, appearance of the prosthesis, pain and HADS score.	Prosthetic usage: • 43/60 (72%) used their prosthesis regularly • 27/80 (34%) had stopped using the prosthesis (includes 20 non-responders) Prosthetic appearance: 46/60 (77%) were satisfied Pain: Phantom limb pain: 36/60 (60%), residual limb pain 29/60 (48%). 27/60 (45%) reported pain in the neck, back and contralateral shoulder. Psychological state: 18/60 (30%) showed significant HADS anxiety scores. 11/60 (18%) showed significant HADS depression scores. Pain and anxiety or depression were not significantly correlated.	Data not analysed statistically.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: 34% of patients rejected their prosthesis and many who continue to wear them do not find them useful in daily life. Rehabilitation services should focus prosthetic and non-prosthetic training to achieve maximal independence.		

Table 9.b Does specialist rehabilitation (physiotherapy and occupational therapy) improve outcomes for people with sarcoma?

Abbreviations: GCT, giant cell tumour; LSS, limb sparing surgery; CPM, continuous passive motion; ROM, range of motion; STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Gudas (2000)	To discuss the particular rehabilitation requirements of patients with sarcoma.	Unsystematic review.			Author's conclusions: Treatment options are now often quality of life driven (limb sparing surgery vs. amputation). More intense aggressive exercise based rehabilitation may be indicated in some patients but not others. An experienced physiotherapist, trained in handling the post surgical sarcoma patient, can do much to assure maximum function and potential.		4-
Heath (1999)	To discuss the rehabilitative needs of children with cancer though the example of a patient with Ewing's sarcoma.	Case report.	The case history of an 11 year old boy with Ewing's sarcoma of the distal femur is discussed. UK	Rehabilitative needs.	Rehabilitative needs were identified and a formal plan drawn up: The patient experienced weight loss, nausea and vomiting and was referred to a dietitian for assessment to ensure that adequate nutrition was obtained. The patient was referred to a physiotherapist to assist in maximising levels of mobility and fitness. The patient was instructed about minimising the risk of pathological fracture, and given pain assessment and analgesia. The patient was also referred to a play specialist whose role was to prepare children for investigative and supportive treatments. Play was used to help children express their anxiety and		4+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					assist them in the development of coping strategies. Author's conclusions: Some nursing staff argued that development of a formal rehabilitation plan was time consuming, and that adequate rehabilitation would have happened anyway. Others, however, commented that the development of the plan was a useful learning experience. A formalised rehabilitation plan may improve service delivery by more accurately targeted care.		
Parsons & Davies (2004).		Unsystematic review.			Author's conclusions: A literature review of STS rehabilitation reveals that most studies have focused on disability assessment, with few papers describing or evaluating rehabilitation interventions commonly employed in STS. Clinicians are forced to extrapolate findings from other patient populations in order to evaluate the effectiveness of specific rehabilitation strategies. There is strongest support for complex decongestive physiotherapy (targeting lymphoedema) and aerobic exercise interventions (aimed at alleviating cancer related fatigue and psychosocial consequences). The most poorly researched topic is rehabilitation for genitourinary disability (both incontinence and sexual dysfunction).		4+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Mankin *et al.* (2004)	To assess the long-term effect of connective tissue cancer treatment on clinical, social, and psychological aspects of the lives of surviving patients.	Cross-sectional study.	Questionnaire sent to 299 patients with high osteosarcoma and 275 with giant cell tumour (GCT) identified from the medical records (1982 onwards) of a single institution. Questionnaires were returned from 180 patients with osteosarcoma and 111 with GCT. Results from 94 patients with osteosarcoma (average age 39±19 years) and 60 with GCT (average age 40±7 years) were analysed. USA	General health status, and reported physical limitations. Measured using an ad-hoc questionnaire.	58/94 (62%) of patients with osteosarcoma and 25/60 (42%) of patients with GCT perceived physical limitations. Most commonly reported limitations in those with osteosarcoma were: limp when walking 52/94 (55%), difficulty with stairs 43/94 (46%), inability to run 15/94 (16%), inability to walk well 11/94 (12%) and unable to do sports 10/94 (11%). For patients with GCT: 25/60 (42%) reported difficulty with stairs, 20/860 (33%) limped when walking, 9/60 (15%) could not run and 6/90 (7%) could not do sports. 44/94 (46%) of patients with osteosarcoma and 19/60 (32%) of patients with GCT participated in physical exercise programs. Physiotherapy was received by 65/94 (69%) of patients with osteosarcoma and 38/60 (63%) of those with GCT.	Comparisons are made between patients with giant cell tumour and osteosarcoma, but the justification for this is not stated. Authors admit that their questionnaire has not been validated. No correction made for multiple statistical comparisons.	3-
Frieden *et al.* (1993)	To present a descriptive study of the surgical course and rehabilitation outcome of patients with bone sarcoma undergoing LSS.	Case series.	17 patients treated for osteosarcoma (n=14) or Ewing's sarcoma (n=3) of the lower extremity. Patients were treated with surgical resection and expandable endoprosthesis. Age ranged from 6 to 17 years (average 12 years). Patients were identified from the records of a single institution. USA	ROM, pain, and ambulation.	Post-operative rehabilitation began the day after surgery with active exercises for the unaffected extremities. CPM (and later stretching) was used to maximize ROM in the affected limb. After discharge from hospital patients continued with outpatient or home physiotherapy. After each lengthening of the prosthesis most patients required a brief course of physiotherapy to correct gait patterns. ROM: Decreased ROM was noted in 6/17 (35%) of patients. Authors suggest that adherence to exercise program was related to ROM, but no data are presented.		3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Pain: Mild to moderate pain was reported by 6/17 (35%) of patients. Ambulation: 7/17 (41%) walked without the aid of orthoses. Authors state that, in addition to surgical technique, time devoted to ambulation practice after surgery was a factor contributing to independent gait, but no data are presented. 16/17 patients returned to school. All were restricted from high impact sports. Authors' conclusions: Children undergoing LSS have special needs including early mobilisation, gait training, adjustment to repeated hospitalisations and continued follow up to monitor their activity restriction.		
Pritchard (1981)	To describe a post-amputation rehabilitation program for children with sarcoma.	Expert opinion.	The program described is that of the Mayo Clinic Department of Orthopaedics around 1979. USA		The child amputee rehabilitation program included patient education consisting of films, prosthetic models and visits by other patients with limb loss due to cancer. Ambulation training was done by a team based in an amputee clinic. Author stresses that rehabilitation should be continually promoted and not relegated to a secondary position during adjuvant therapy. A biomechanics gait laboratory was also used to correct poor gait habits.	Old paper before limb salvage surgery became widespread.	4-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Griffith (1981)	To identify the special needs of the paediatric tumour patient within the context of the prosthetic clinic. To identify those conditions influencing rehabilitation outcome.	Expert opinion and case report.	A case history of an 18 year old female who underwent a trans-femoral amputation following osteosarcoma was included.	Predictors of rehabilitation outcome.	Predictors of unfavourable rehabilitation outcome: poor presurgical condition, high amputation level, post surgical complications, and residual limb problems. Predictors of positive rehabilitation outcome: early prosthetic fitting, mobility and training; positive family participation and attitude. Principles of amputee rehabilitation are discussed: presurgical initiation, the immediate post operative period, training and long term care. The measurement of the effectiveness of rehabilitation services is considered and several outcome measures for audit are proposed.	Old paper before limb salvage surgery became widespread.	4-

Palliative care

The question

Do palliative care specialists with an interest in sarcomas enhance quality of life for people with sarcoma?

Nature of the evidence

No evidence about the palliative care of people with sarcomas was identified. NICE guidance on *Improving Supportive and Palliative Care for Adults with Cancer* reviewed evidence for the configuration of palliative care services, and is likely to be applicable to people with sarcoma.

Summary of the supporting evidence for the recommendations

In the absence of sarcoma specific evidence, the relevant evidence reviewed in NICE guidance on *Improving Supportive and Palliative Care for Adults with Cancer* is summarised below.

Evidence from systematic reviews supports the effectiveness of specialist palliative care teams for the control of pain and symptoms of people with cancer. People cared for by specialist teams were more satisfied than those cared for elsewhere.

Evidence from systematic reviews suggests that specialist palliative care delivered at a patient's home or in a hospice can be as effective as conventional hospital-based care in the control of pain and symptoms and in terms of patient satisfaction.

There was insufficient evidence to recommend the ideal structure of a specialist palliative care team but patient outcomes tended to be better with specialist palliative care teams made up of multidisciplinary trained staff.

Two randomised controlled trials reported that employment of a nurse co-ordinator, who provided a link between patients and the health services, reduced the number of days spent in hospital by the patient and the number of home visits by the community care team.

Follow up

The questions

a) For how long should people with sarcoma be followed up and by what method?

b) What is the impact of follow up of people with sarcoma on their survival and disease recurrence?

c) Does surveillance improve outcomes for people predisposed to sarcoma?

Nature of the evidence

a) For how long should people with sarcoma be followed up and by what method?

There was a lack of research evaluating follow up strategies for people with STS. Most of the studies identified were reports of follow up routines for people with extremity STS. All were American, except a multi-centre European study (Langer *et al.* 2004), and Italian (Filiberti *et al.* 1993) and UK studies (Jeys *et al.* 2003). Applicability of the evidence to the UK setting was questionable.

Three studies of poor quality were published from a 1997 survey of follow up practices in 318 members of the Society of Surgical Oncology who treated and provided postoperative follow up for people with extremity STS (Beitler *et al.* 2000; Sakata *et al.* 2002; Sakata *et al.* 2003). One systematic review of poor quality compared the costs of current follow-up practices in physicians treating people with extremity STS (Goel *et al.* 2004).

Two observational studies of good quality compared the effectiveness of tests used during follow up of people with extremity STS (Whooley *et al.* 1999; Whooley *et al.* 2000). The effectiveness of routine follow-up testing was also considered in an observational study of 643 patients at a UK sarcoma treatment centre (Jeys *et al.* 2003). Two observational studies of good quality examined the cost effectiveness of chest X-ray and chest CT in the staging of patients with primary T1 (Fleming *et al.* 2001) and T2 (Porter *et al.* 2002) STS.

Two clinical guidelines (American College of Radiology (ACR) 2002; Demetri & Kiel 2004) and one unsystematic review proposed surveillance strategies for STS (Patel, Zagars, & Pisters 2003).

A prospective observational study (Langer *et al.* 2004) recorded late effects in the year following cessation of therapy in clinical trials for Ewing's sarcoma, osteosarcoma or STS following treatment, in a group of German, Austrian and Swiss patients. Evidence about late effects following treatment for cancer in children and young people, is reviewed in the NICE guidance on *Improving Outcomes in Children and Young People with Cancer*.

Evidence on the acceptability of follow up to people with sarcoma was limited to a small cross-sectional study of 30 Italian patients (Filiberti *et al.* 1993) published in abstract form.

b) What is the impact of follow up of people with sarcoma on their survival and disease recurrence?

None of the studies described above compared these outcomes in patients followed-up using different strategies. It was not possible to estimate the impact of follow up on patient survival and disease recurrence.

c) Does surveillance improve outcomes for patients predisposed to sarcoma?

No studies compared outcomes in people at risk of sarcoma who were actively monitored with those who did not receive surveillance. Several studies discussed the surveillance of groups predisposed to sarcoma and were included as evidence. These studies do not represent an exhaustive list of the genetic syndromes or other risk factors predisposing to sarcoma.

A UK cohort and case-control study of good quality (Hawkins *et al.* 1996) estimated the risk of primary bone cancer following radiotherapy or alkylating agent chemotherapy for childhood cancer. US observational studies of good quality (Abramson *et al.* 2001) described bone and soft tissue tumours in survivors of retinoblastoma and the incidence of second malignant neoplasms in survivors of osteosarcoma (Aung *et al.* 2002).

A UK observational study of good quality (Porter *et al.* 2004) reported the risk of malignant change in people with hereditary multiple exostoses. A US study reported the incidence of chondrosarcoma in people with enchondromatosis (Schwartz *et al.* 1987).

A French consensus based guideline for the management of people with Li-Fraumeni syndrome (Frebourg *et al.* 2001) discussed the role of surveillance in this group.

Summary of the supporting evidence for the recommendations

a) For how long should people with sarcoma be followed up and by what method?

A surveillance strategy with more visits should, on average, detect disease relapse earlier than one with fewer visits. Practical constraints, however, mean that the number of follow-up visits is limited The optimal follow-up strategy would incorporate the time dependent risk of recurrence, the cost of follow up and an estimation of the benefits of the early detection of recurrence (is there an effective treatment and is it important to initiate this treatment before the patient becomes symptomatic?).

No such follow-up strategy was identified for people with sarcoma and the development of such a model was beyond the scope of this guidance. The lack of studies comparing follow-up strategies for people with sarcoma, in terms of health outcomes, supports the recommendation for research into appropriate follow-up protocols for each tumour type and location.

Current situation

The study of Goel and co-workers (Goel *et al.* 2004) identified eleven papers in which experts recommended 26 strategies for the follow up of extremity STS. There was agreement on the place of routine clinical examination and chest X-ray in follow-up. There was disagreement, however, over the role of routine chest CT and over the best method for regular imaging of the primary site.

The 1997 survey of US surgeons (Beitler *et al.* 2000; Sakata *et al.* 2002; Sakata *et al.* 2003) about post-treatment follow-up protocols for extremity STS showed considerable variation in strategies. Clinical examination and chest X-ray were the most frequently performed follow-up tests. Approximately half the surgeons ordered MRI or CT imaging of the primary site in the first post-operative year. The frequency of follow up visits was usually related to an estimated risk of recurrence, based on the time elapsed since treatment, tumour characteristics and surgical margins.

Consensus based guidelines for the follow up of people with sarcoma, stratified by the grade and site of the original tumour, have been proposed by the American National Comprehensive Cancer Network (Demetri & Kiel 2004) and the American College of Radiology (American College of Radiology (ACR) 2002).

Effectiveness of follow-up strategies in the detection of recurrence

Whooley and co-workers (Whooley *et al.* 2000) reported the effectiveness of routine follow up for the detection of recurrence in people with primary extremity STS at a US treatment centre. 29/141 patients developed a local recurrence, all but one of which was discovered during physical examination. 13/29 of the local recurrences were detected either by the patient or a primary care doctor between follow-up visits.

None of the 21 patients who presented between follow-up visits with symptomatic pulmonary metastases were considered candidates for potentially curative surgical resection of their metastases. Resection of pulmonary metastases was performed for 24 of the 36 patients whose asymptomatic recurrence was discovered by surveillance chest X-ray or staging CT scan.

In the UK study of Jeys and co-workers (Jeys *et al.* 2003) 15% of local recurrences in people with STS were discovered at a follow-up appointment and 70% were detected by the patient between surveillance visits. For those with bone sarcoma, 36% of local recurrences were picked up at surveillance visits and 57% were discovered by the patient.

Two studies compared routine chest CT with selective chest CT (performed only after a suspicious chest X-ray) for the detection of pulmonary metastases in people with primary T1 (Fleming *et al.* 2001) or T2 (Porter *et al.* 2002; Porter *et al.* 2002) STS. Although routine chest CT was more sensitive than selective chest CT, authors concluded it would only be a cost effective follow-up strategy for the highest risk patients.

Patients' views on follow up

The impact of follow up on patients' psychological wellbeing is an important consideration, since visits could give reassurance but may also cause unnecessary anxiety. Evidence on the acceptability of follow up to people with sarcoma was limited to a small cross-sectional study of 30 patients (Filiberti *et al.* 1993). Although patients reported anxiety before follow-up visits, 80% said that the visit itself was a positive experience.

Late effects of treatment

Evidence reviewed in the NICE guidance on *Improving Outcomes in Children and Young People with Cancer*, suggests that most patients have at least one moderate to severe adverse health outcome following treatment for childhood cancer. The study of Langer and co-workers (Langer *et al.* 2004) noted cardiotoxicity in 12%, ototoxicity in 7% and nephrotoxoticty in 1% of people with bone or soft tissue sarcoma, in the first year after treatment in a clinical trial.

b) What is the impact of follow up of people with sarcoma on their survival and disease recurrence?

There was insufficient evidence to estimate the effect of follow up on survival and disease recurrence in people with sarcoma.

c) Does surveillance improve outcomes for people predisposed to sarcoma?

There is good evidence that certain groups face an increased risk of developing sarcoma but the lack of relevant studies means it is not possible to say whether surveillance will improve their outcomes. Several authors have concluded that the increased risk of sarcoma in itself is sufficient to justify the surveillance of these

people (Aung *et al.* 2002; Frebourg *et al.* 2001; Hawkins *et al.* 1996; Porter *et al.* 2004; Schwartz *et al.* 1987).

Table 10.a For how long should people with sarcoma be followed up and by what method? What is the impact of follow up of people with sarcoma on their survival and disease recurrence?

Abbreviations: CBC, complete blood count; CT, computerized tomography; FBC, full blood count; H&P, history and physical examination; HPF, high power fields; LFT, liver function tests; MFH, malignant fibrous histiocytoma; MRI, magnetic resonance imaging; PET, positron emission tomography; STS, soft tissue sarcoma.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
American College of Radiology (ACR) (2002)		Guideline.			For malignant or aggressive musculoskeletal or soft tissue tumours follow up for: 1) LUNG METASTASES: post operative examination at 3–6 months, follow up at 6–12 month intervals for 10 years. Imaging using CT or chest X-ray. 2) BONE METASTASES: examination and follow up only if symptomatic, using bone scan. 3) LOCAL RECURRENCE baseline examination at 2–6 months post operatively, follow up at 6–9 monthly intervals. No consensus for duration of follow up, in the absence of clinical signs 3 years may be sufficient. Imaging method MRI (or plain radiograph if there is significant hardware present). Authors' conclusions: Authors suggest that MRI, CT, and PET are all needed to identify the extent of disease in follow up (data for PET are encouraging but still unproven). They admit this is a costly suggestion and that others have not yet advocated this extensive follow-up protocol in a routine clinical setting.		4

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Kane III (2004)	To examine the factors predictive of recurrence for STS, the role of salvage therapy, and the data in support of current surveillance strategies.	Review article.			For STS, patient education and office visits with thorough history and physical examination will detect the vast majority of recurrent disease. Routine surveillance imaging is only of significant benefit if the risk for asymptomatic recurrence is high or if other factors make clinical assessment difficult.		4
Demetri & Kiel (2004)		Clinical guideline for the management of STS.			Follow up for the detection of local recurrence: The National Comprehensive Cancer Network (NCCN) guideline suggests that stage 1 extremity STS tumours should be followed with routine H&P every 3 to 6 months for 5 years and then annually. Baseline imaging of the primary site should be considered, and annual imaging of the primary site considered based on the estimated risk of recurrence. The NCCN guideline states that for large or high grade tumours H&P should be done every 3-4 months for 2 years, then 6 monthly for 3 years then annually. Imaging (MRI or CT) should be considered every 4 to 6 months for 3 years and then annually. Long term annual follow-up is indicated. The NCCN guideline states that for patients with GIST should have a H&P and abdominopelvic CT scan every 3 to 6 months for 5 years and annually thereafter. Patients with retroperitoneal or visceral STS should have a follow-up physical examination every 3 to 6 months and be considered for an abdominopelvic CT scan every 6 months. Follow up for the detection of distant recurrence The NCCN guideline states that for stage 1 extremity STS tumours, chest x-ray should be considered every 6-12 months. For large or high		4+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					grade tumours chest x-rays should be performed every 3 to 6 months for 5 years, then annually. The NCCN guideline states that patients with GIST should receive an abdominopelvic CT scan every 3 to 6 months and annually thereafter. Patients with retroperitoneal or visceral STS should be considered for an abdominopelvic CT scan every 6 months.		

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Whooley *et al.* (2000)	To evaluate the effectiveness of follow-up tests for detecting first local and distant recurrences in patients with primary extremity STS.	Retrospective case series.	174 adults with primary extremity STS treated between 1982 and 1992 at a single treatment centre. USA		After treatment for primary STS patients were observed: • every 3 months for 2 years • every 4 months in the 3rd year • every 6 months in the 4th and 5th years • annually thereafter. Each visit consisted of patient history and physical, complete blood count, blood chemistry and chest X-ray. At the discretion of the surgeon some patients had annual MRI or CT of the primary tumour site. Some patients had a chest CT as a confirmatory test or for preoperative planning. Of 141 patients who were assessable, 29 patients developed local recurrence and 57 developed distant recurrence. All but one of the local recurrences was detected on the basis of an abnormal physical examination. Of the 29 patients who developed local recurrence, 25 were resected. Distant metastases were detected because of symptoms in 21 cases. Of the 36 asymptomatic lung recurrences, 30 were detected by follow up chest X-ray. Of the 36 asymptomatic lung recurrences, 24 patients underwent metastasectomy. The positive and negative predictive values of surveillance chest X-ray were 92% and 97%, respectively. Laboratory testing never led to the detection of recurrence.	Same case series as Whooley et al. (1999). Authors conclude that close surveillance by clinical assessment and chest X-ray is appropriate for follow up in patients with primary extremity STS. They argue that the role of CT and MRI is in those patients with deeply situated tumours. Their current follow-up regime for patients with deep high-risk tumours involves more intensive cross-sectional imaging than reported in this study. Routine laboratory blood tests were ineffective for detection of recurrence.	3+
Sakata *et al.* (2002)	To investigate whether the date of completion of formal surgical training affects choice of surveillance	Cross-sectional questionnaire.	1592 members of the Society for Surgical Oncology were surveyed. Of the 716 respondents 318 performed sarcoma surgery and provided follow-up	Number and type of tests used for follow up in years 1, 2, 3, 4, 5 and 10 after resection. 4 scenarios: small low-grade, large low-grade, small high-grade and	Data from all 4 scenarios were combined in analysis because the variation was small. Surgeons who completed training more than 30 years ago ordered erythrocyte sedimentation rate more frequently ($p < 0.001$). Surgeons in the 21–30 year category ordered extremity X-ray and	Uses the data from Bietler et al (2000). Surgeons' age is presented as a surrogate measure for the effectiveness of continuing medical education. However older surgeons have the same access to journals, courses and	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
	strategy.		care. USA	large high-grade tumours.	bone scan more frequently ($p < 0.05$), but absolute differences among age groups were quite small. Older surgeons were also significantly more likely to believe that follow up is clinically worthwhile. Authors' conclusions: The post treatment surveillance practice patterns of the members of the Society of Surgical Oncology caring for patients with extremity STS vary only marginally with the length of time since completion of training.	conferences. Not clear how many of the surgeons dealing with sarcoma are represented in the study. Analysis of variance appears to have been used inappropriately on non-parametric data.	
Sakata *et al.* (2003)	To investigate whether tumour grade and size account for the considerable variation in the intensity of follow up after potentially curative surgery for extremity STS.	Cross-sectional questionnaire.	1593 members of the Society for Surgical Oncology were surveyed. Of the 716 respondents 318 performed sarcoma surgery and provided follow-up care. USA	Number and type of tests used for follow up in years 1, 2, 3, 4, 5 and 10 after resection. 4 scenarios: small low-grade, large low-grade, small high-grade and large high-grade tumours.	Office visit, complete blood count, liver function tests, chest X-ray, chest CT, extremity CT, and extremity MRI were ordered significantly more frequently with increasing tumour grade and size. Authors' conclusions: Tumour grade and size significantly impacted physician practice patterns in post-treatment follow up, although the degree of variation attributable to these variables was modest.	Uses the data from Bietler et al (2000). chest X-ray was performed less than 2 times a year on average. Lab tests were rarely performed (on average less than once a year). Not clear what percentage of practising surgeons dealing with sarcoma are represented in the study. Analysis of variance appears to have been used inappropriately on non-parametric data.	3-
Langer *et al.* (2004)	A pilot study to investigate late effects in patients with Ewing, osteosarcoma or soft tissue sarcoma.	Case series.	230 patients treated between 1998 and 1999 according to the sarcoma protocols COSS-96, CWS-96, and EICESS-92. 114 osteosarcomas, 80 STS and 64 Ewing sarcomas GERMANY, AUSTRIA, SWITZERLAND	Percentages of patients who experienced: cardiotoxicity, nephrotoxicity or ototoxicity 1 year after cessation of chemotherapy.	Cardiotoxicity: 16/129 (12%) patients treated with doxorubicin and 1/19 (5%) treated with epirubicin exhibited a reduced systolic heart function (fractional shortening (FS) <29%). Three patients required cardiac drug therapy. Ototoxicity: In 5/73 (7%) patients treated with cisplatin a hearing deficit <4 kHz (>20 dB) was found. One patient needed a hearing aid. Nephrotoxicity: 2 of 214 (1%) patients treated with ifosfamide suffered from a tubulopathy, which required supplementation therapy. Incidence of hypomagnesaemia was significantly	Multi-centre study involving 82 hospitals (3 clinical trials). Results for sub-groups (Ewing vs. STS vs. osteosarcoma) were not reported separately. Follow up of 1 year could underestimate the risk of late effects in this group. Follow up was incomplete: only 73/230 patients had their hearing tested, 149/198 of patients treated with doxorubicin or epirubicin had an echocardiogram and 124/230 of the patients had urea,	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					increased in patients additionally treated with cisplatin.	creatinine and electrolytes tests. It may have made clinical sense to omit certain tests but it makes it difficult to estimate the true risk of late effects in this group.	
Patel *et al.* (2003)	To present a clinical guideline for the follow up of adult STS.	Expert consensus, review article.			Authors' conclusions: Patients with low-risk STS who have undergone curative therapy could be followed with a H&P and chest X-ray at 3 to 4 month intervals for 2 years and yearly thereafter. CT imaging should be individualised based on the reliability of physical examination and suspicion for deep-seated recurrence. Patients with non-extremity sites frequently require cross-sectional imaging for follow up. Patients with low-risk of recurrence could stop surveillance after 5-10 years. Patients with high-risk STS could be followed with a H&P, lab tests, chest X-ray and MRI or CT every 3 months for 2 years, every 4 months for 2 years and every 6 months for the 5th year and yearly thereafter.		4
Beitler *et al.* (2000)	To determine the current follow up practices of physicians caring for patients with extremity sarcomas.	Cross-sectional questionnaire.	1592 members of the Society for Surgical Oncology (SSO) were surveyed. Of the 716 respondents 318 performed sarcoma surgery and provided follow-up care. USA	Number and type of tests used for follow up in years 1, 2, 3, 4, 5 and 10 after resection. 4 scenarios: small low-grade, large low-grade, small high-grade and large high-grade tumours.	Wide variation between follow-up routines. Office visits and chest X-ray were the most frequently performed items for each of the years. The frequency of office visits and chest X-ray increased with tumour size and grade and decreased with postoperative year. Complete blood count and liver function tests were the most commonly ordered blood tests. Many respondents did not order any blood tests routinely. Imaging studies of the extremities (MRI more often than CT) were performed on the majority of patients with large (> 5 cm) low-grade lesions and on both large and small high-grade lesions during the first postoperative year.	The questionnaire is a surrogate measure of follow up, an observational study would provide a more direct measure. Only members of the SSO were included, not clear what percentage of surgeons dealing with sarcoma in the USA are represented in the study. Full data only provided for high-grade tumours >5cm. Only descriptive statistics are used for follow-up data.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Authors' conclusions: Postoperative sarcoma surveillance strategies utilised by members of the SSO rely most heavily on office visits and chest X-ray. Tumour grade, tumour size, and postoperative year affect surveillance intensity. The optimum follow-up strategy remains to be determined.		
Goel *et al.* (2004)		Systematic review.	33 papers describing 54 follow-up strategies for STS.	Cost of follow up for 5 years post-treatment (calculated using Medicare-allowed charges as a proxy).	Total charges (in 2003 currency) ranged from $485 (£300) for follow up of low-grade sarcoma to $21,235 (£13,000) for follow up of high-grade sarcoma. The average charge for these 54 strategies was $6,401 (£3920). Physical examination and chest X-ray were the most commonly used screening modalities. Authors' conclusions: This study shows wide disparity in the costs of 54 specific methods of following STS patients. Clinical trials are needed to identify an optimal surveillance strategy, balancing gains in survival, quality of life, costs, and societal willingness to expend resources.	The costs of positive follow up test results were not considered, or the psychological impact of follow up on patients. Literature search not comprehensive, only Medline 1982–2003 searched (also review articles and textbooks). English language only. Study design was reported but not taken into account in analysis.	2-
Whooley *et al.* (1999)	To provide an evidence based rationale for the follow up of STS.	Case series.	174 patients with primary extremity STS, treated between 1982 and 1992 at a single institution. 49% of patients had high-grade tumours and median tumour size was 8cm. USA	Cost per non-quality adjusted life year (NQALY) saved by follow up.	Patients were followed up every 3 months in the first 2 years, every 4 months in the 3rd year, and every 6 months in years 4 and 5 post treatment. Annual follow up for life was recommended after 5 years. At each visit the following tests were carried out: H&P, FBC, electrolytes, LFT and chest X-ray. MRI or CT of the primary site was performed annually, chest CT was performed after equivocal chest X-ray. 27 local recurrences occurred at a median of 14	Same case series as Whooley et al. (2000). Unclear how the authors arrive at their estimate of years of life gained due to follow up. There is no control group in this study. Cost effectiveness is calculated using no follow up as a comparison. It is difficult to	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					months post treatment. 26 detected by physical exam, 1 by imaging. 83% were resectable. There were 57 distant recurrences at a median of 18 months post treatment. 21 were detected following symptoms, 30 chest X-ray and 6 chest CT. Surveillance with blood tests did not detect any recurrences, CT and MRI of the primary site detected 1 local recurrence. The cost effectiveness of chest X-ray surveillance was $30,000 per NQALY in 1997 currency, comparing well with the suggested $50,000–$100,000 cut-off values. Authors' conclusions: Clinical assessment of patient symptoms, chest X-ray, and physical examination are effective strategies for follow up of extremity STS. Chest X-ray also appears to be cost-effective, at least for high-grade extremity STS.	argue that no follow up is the standard for high-grade STS. Authors admit that MRI and CT technology have improved in the 20 years since the start of this analysis. The sensitivity of MRI and CT for recurrence may be underestimated. Poor sensitivity of MRI/CT for local recurrence in this study could also be due to infrequent scanning.	
Fleming *et al.* (2001)	To evaluate the use and yield of chest X-ray and selective chest CT to screen for pulmonary metastases in patients with T1 STS.	Retrospective case series.	125 adult patients with T1 (size <5cm) primary extremity STS. All patients presented to a single institution between 1984 and 1992. USA	The clinical and cost effectiveness of each imaging strategy.	2 imaging strategies were compared retrospectively: chest X-ray alone vs. chest X-ray + chest CT. More patients with high-grade tumours received CT scans (based on clinical suspicion). 1/51 patients in the chest X-ray + chest CT group had a chest X-ray that was suspicious for metastatic disease, the subsequent chest CT confirmed metastatic disease. None of the 74 patients staged with chest X-ray alone had pulmonary metastatis identified. No patients with chest X-ray-occult metastases were identified by chest CT.	Too few metastatic cases to compare the diagnostic accuracy of the 2 strategies. If the chest CT was assumed to be the gold standard then it was not applied to a subset of the patients. It is impossible to tell whether chest X-raymissed lung metastases in these cases. 19/125 of the patients went on to develop lung metastases.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					The addition of CT to chest X-ray screening added an extra $59,772 per case of pulmonary metastasis identified. Cost of chest X-ray was $162 and CT was $1172. Authors' conclusions: The yield and cost data demonstrate that the use of chest CT in this patient population is expensive and rarely provides additional relevant clinical information.		
Porter *et al.* (2002)	To determine the yield and cost–effectiveness of routine vs. selective CT scanning for staging of patients with T2 STS.	Retrospective case series.	600 adult (>16 years old) patients with primary T2 (> 5cm) STS. Primary tumours of the thorax and chest wall were excluded. Only patients who had both chest X-ray and chest CT were included. All patients presented to a single institution between 1996 and 1999.	Presence of pulmonary metastases, as identified by CT scan. Sensitivity of diagnostic techniques: CT and chest X-ray. Cost effectiveness of CT and chest X-ray.	42% of patients had tumours >10cm and 69% of tumours were high grade. Comparison of strategies: Routine chest CT cost $1301 per patient and identified 115 (19.2%) of patients with lung metastases (M1). Selective chest CT involved a CT scan only if initial chest X-ray was suspicious. It cost $418 per patient and identified 96 patients (16%) with lung metastases. The selective CT approach identified 83.5% of patients with lung metastases. The incremental cost effectiveness ratio, calculated as the cost per additional patient identified by routine vs. selective chest CT was $27,594. Further cost effectiveness analysis was performed for sub-groups of tumour grade (low vs. high) and location (extremity vs. retroperitoneal). Authors' conclusions: For patients with T2 STS, routine chest CT was	CT was considered the gold standard test, lung metastases were not confirmed histologically. The possibility of false positives or negatives in the chest CT results was not considered. This would affect the estimation of cost-effectiveness.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					the most cost effective in patients with high grade or extremity lesions. The findings of this study do not support the routine use of chest CT scanning in all patients with T2 STS.		
Filiberti *et al.* (1993)	To assess if intensive follow up causes psychological distress to patients with sarcoma.	Cross–sectional study.	30 patients treated for STS. Time since treatment ranged from 6 months to 2 years. ITALY	Personality test (16 P.F. Questionnaire) and patients opinions about the follow-up schedule.	Follow up consisted of a chest X-ray and physical exam every 2–3 months. 24/30 (80%) of the patients reported their experience of the follow up visit as at least "positive". Anxiety was reportedly experienced for between 1 to 30 days prior to the follow up visit (median 7 days). Authors' conclusions: Follow up visits are not necessarily distressing and sometimes the patient may feel the need for them on a regular basis. Psychological factors should be considered when formulating a follow up strategy.	Abstract only. Little detail about the study population. Unlikely that cross sectional design is the most appropriate for the research question.	3-
O'Donnell *et al.* (1997)	To describe current follow-up practices of institutions treating STS.	Unsystematic review.	The follow up practices of 5 STS treatment centres were described: 3 from the USA, 1 from Japan and 1 from the UK.	The annual frequency and type of follow up tests used during the first 5 years of follow up of patients with STS.	Each of the 5 institutions describes its own follow up routines. A table of frequency of tests vs. institution was presented. All centres (except for the UK one) reported a range of strategies depending on the size of the tumour and its location (extremity vs. intra-abdominal or retroperitoneal). Office visit: All centres used office visits (H&P) in follow up. Frequency ranged from 2–7 visits per annum in the 1st year to 1–2 per annum in the 5th year. Chest X-ray: All centres used chest X-ray. Frequency ranged	Not stated why the 5 centres were chosen. It is unclear how the reported follo- up regimes correspond to actual practices in these institutions.	4+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					from 1–4 chest X-ray per annum in the 1st year to 1–2 in the 5th year Chest CT: Chest CT was done routinely in 2/5 centres, the other centres used chest CT only if metastatic recurrence was suspected. Abdominal CT: Abdominal CT was used routinely in the follow up of retroperitoneal or deep seated STS in 3/5 centres. Site MRI: 3/5 centres routinely imaged the primary site each year. The UK centre performed a baseline MRI 1 year after surgery and then only used MRI if recurrence was suspected based on clinical findings. CBC & LFT: CBC was done at all centres except the Japanese one. LFT was only performed routinely at 2 US centres.		
Jeys *et al.* (2003)	To assess the effectiveness of follow up protocols at a sarcoma treatment centre.	Case series.	643 patients with soft tissue or bone sarcoma treated between 1990 and 1995, identified from the records of a single sarcoma treatment centre. Patients were involved in a follow up programme of regular clinical examination, chest X-ray and radiological imaging. UK	The method of detection of local and distant recurrences.	Local recurrence occurred in 14% of cases and 34% developed metastases. Cumulative 10 year survival was 59%. 15% of local recurrences were picked up during follow up visits, 70% by the patients between visits. The other 15% are unaccounted for. For bone sarcomas 36% were picked up at surveillance visits, 57% by the patient, 6% unaccounted for. Pulmonary metastasis was developed by 82% of patients. 78% were identified by surveillance chest X-ray of which 83% were asymptomatic	Conference presentation - only abstract available. Study design does not allow the sensitivity of follow up tests to be estimated.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					and 34% went on to have metastectomy. A third of non-pulmonary metastases were detected during follow up and all were symptomatic. Authors; conclusions: Clinical examination and chest X-ray were found to be valuable tools in the follow up of patients with sarcoma, but patient education and open access to clinics is also important.		

Table 10.b Does surveillance improve outcomes for patients predisposed to sarcoma?

Abbreviations: AML, acute myeloid leukaemia; CI, confidence interval; CNS, central nervous system; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; HME, hereditary multiple exostoses; MFH, malignant fibrous histiocytoma; MRI, magnetic resonance imaging; NOS, not otherwise specified; RR, relative risk; SEER, Surveillance, Epidemiology and End Results; SMN, second malignant neoplasm; STS, soft tissue sarcoma; U/S, ultrasound.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Hawkins *et al.* (1996)	To investigate the incidence and aetiology of second primary bone cancer after childhood cancer.	Cohort and case control.	COHORT STUDY: The study used the population based National Registry of Childhood Tumours. The cohort included all patients diagnosed with childhood cancer between 1940 and 1983, who survived at least 3 years after diagnosis (n=13,175). CASE-CONTROL STUDY: 55 patients developed second primary bone cancer, for each case 4 matched controls were selected from the cohort. UK	Incidence of bone cancer after childhood cancer.	Cohort study: 55 patients developed a second primary bone cancer (45 osteosarcomas, 3 fibrosarcomas, 2 chondrosarcomas, 1 each of angiosarcoma, round-cell sarcoma, MFH, sarcoma NOS and Langerhan's cell histiocytosis). The percentage of 3 year survivors developing bone cancer did not exceed 0.9%, except following heritable retinoblastoma (7.2%), Ewing's sarcoma (5.4%) and other malignant bone tumours (2.4%). Case-control study: The risk of bone cancer increased linearly with cumulative dose of radiation to the bone ($p<0.001$). Exposure to less than 10 Gy was associated with only a small increased RR of bone cancer (RR = 0.7; 95% CI = 0.2–2.2). Risk of bone cancer also increased linearly with increased exposure to alkylating agents ($p = 0.4$). Authors' conclusions: Survivors of childhood cancer should be assured that the risk of developing a secondary bone cancer is low (0.9%). Higher risks found for bone cancer following other specific rare types of childhood cancer provide a rational basis for surveillance.	Not strictly a cohort study given the long interval of entry into the group (1940–1983) a time in which treatment and exposure would have changed greatly. The reported risks may not be valid for patients treated recently.	2++

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Abramson *et al.* (2001)	To investigate the incidence, timing, pattern and distribution of 3rd, 4th and 5th tumours in patients with retinoblastoma.	Retrospective case series.	211 patients with retinoblastoma who developed a second (non-ocular) tumour. Patients were selected from a case series of 1506 from the records of an Ophthalmic Cancer Centre. Only those with sufficiently complete clinical data were included in the analysis. USA	Development of a 3rd or 4th tumour and survival data.	Second tumour was in the radiation field (head and neck) in 122/211 (58%) of cases. Site of second tumour: Soft tissues of head 44 cases (24%), skull 33 (18%), skin 27 (15%), bones 20 (11%), brain 14 (8%) and other 45 (25%). 5 year survival after 2nd tumour was 32%, 10 year survival was 25% Third tumour: 28 of the patients developed a third tumour. Site was: soft tissues of head 11 cases (39%), skin 10 (36%), bones 2 (7%) and other 5 (18%). Fourth tumour: Developed in 6 cases. Site of the tumour was bone 2 cases (33%), skin 2 (33%) and soft tissues of the head 2 (33%). Authors' conclusions: Survivors of retinoblastoma in whom second malignant neoplasms develop are at a higher risk for the development of further tumours. A rate of 1% per year of life is a reasonable estimate for patient counselling (e.g. 20% risk of developing a second tumour by age 20, 40% at age 40). Ultimately most bilateral retinoblastoma patients will have multiple cancers that will shorten their life expectancy.	The follow up period (from diagnosis of retinoblastoma) ranged from 2 to 73 years (mean 24 years). Selected only patients with follow up data. If incomplete follow up is associated with death this could underestimate the risk of second tumours.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Aung *et al.* (2002)	To estimate the incidence of second malignant neoplasms (SMN) in survivors of osteosarcoma.	Retrospective case series.	509 patients with primary osteosarcoma. Patients were identified from the records of a single institution between 1973 and 2000. USA	Second malignant neoplasm (SMN).	Median follow up was 8.7 years (range 0.1–25 years). During this time 327 (64%) of the patients survived. 14 (2.8%) of the 509 patients developed a SMN. SEER data were used to calculate standardised incidence ratios (expected incidence for this group was 3.02 cases of SMN). The standardised incidence ratio was 4.6 (95% CI 2.53–7.78, p<0.001). Excluding the 3 patients with history of retinoblastoma or Rothmund-Thompson syndrome, the standardised incidence ratio was 3.64 (95% CI 1.82–6.52, p<0.001). The most common SMN site was the CNS (n=4), there were 2 cases of AML, one myelodysplastic syndrome and one case each of non-Hodgkin lymphoma, pleomorphic sarcoma, leiomyosarcoma, fibrosarcoma, breast carcinoma and mucoepidermoid carcinoma. Authors' conclusions: The incidence of SMN in long term survivors of osteosarcoma was significantly higher than the expected incidence. Although additional follow up is warranted, the successes of treatment regimes involving high-dose chemotherapy outweigh the risks.	Only patients who developed an SMN other than osteosarcoma were included. Chemotherapy and family history were considered as prognostic markers for SMN but a statistical model was not constructed (possibly due to the low event rate). Completeness of follow up is not reported.	3+
Schwartz *et al.* (1987)	To estimate the incidence of secondary chondrosarcoma in patients with enchondromatosis.	Retrospective case series.	44 patients with multiple enchondromas were identified from the records of three institutions between 1923 and 1980. 37 had Ollier disease and 7 Maffucci syndrome. 36 patients were contacted and given a follow up examination. In the 8 patients who had died, evaluation was based on	Incidence of chondrosarcoma or other malignant neoplasm.	Of the 37 patients who had Ollier disease, a low-grade chondrosarcoma developed in 4, an astrocytoma in 1; and a granulosa-cell ovarian tumour in 1. In 4 of the 7 patients who had Maffucci syndrome, there were 6 low-grade chondrosarcomas, 1 high-grade osteosarcoma, 1 pancreatic adenocarcinoma, 1 biliary adenocarcinoma, and 1 astrocytoma. None of the patients in either group died of a skeletal sarcoma, but 4 of 5 patients who had a non-skeletal malignant lesion died.	All the chondrosarcomas observed were low grade; authors note that such tumours may be difficult to distinguish from enchondromas. 7 patients with Ollier disease could not be contacted and were not included. Incidence of malignancy may therefore be underestimated. Small study.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
			autopsy and medical records. USA		Authors' conclusions: From life table analysis of these patients the estimated incidence of secondary chondrosarcoma in Ollier disease is about 25% at the age of 40 years, and malignant degeneration is highly probable in Maffucci syndrome. Periodic surveillance of the brain and abdomen of occult malignant lesions is therefore justified in patients with enchondromatosis.		

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Frebourg *et al.* (2001)	To propose guidelines for the clinical management of Li-Fraumeni syndrome.	Guideline.			Guideline discusses monitoring French patients with Li-Fraumeni syndrome for early detection of malignancy. In infancy, the feasibility of screening for the characteristic tumours of Li-Fraumeni syndrome is variable: screening for STS, due to their ubiquitous location, appears impractical. Patients with osteosarcomas should benefit from early diagnosis due to their high grade nature. Lastly screening for the cerebral tumours does not appear practical. In part because of the evolutionary speed of certain cerebral tumours which would require very frequent monitoring and also because of the problem of access to MRI machines (in France circa 2001). In adulthood screening for breast cancer is of most importance. The theoretical radio sensitivity of patients with germline p53 mutations means that ultrasound or MRI may be more appropriate than mammography, especially in younger women. Authors' recommendations: In childhood, annual clinical follow up by a paediatrician familiar with the syndrome. Women older than 20 years with the syndrome should be screened annually (U/S or MRI) for breast cancer.	Guideline developed by an FNCLCC Li-Fraumeni syndrome working group. Recommendations appear to be based on expert opinion.	4-
Porter *et al.* (2004)	To identify prognostic factors for disease severity and development of sarcoma in HME.	Prospective case series.	172 patients with HME from 78 families. Patients with solitary osteochondromas were excluded. Patients were selected by referral from orthopaedic surgeons, geneticists or presented themselves between 1996 and 2000. UK	Disease severity (functioning and deformity were assed using a scale), number of exostoses and development of sarcoma.	Mutations EXT1 and EXT2 were almost equally common, and were identified in 83% of individuals. There was a wide variation in the severity of disease. The severity of the disease did not differ significantly with gender and was very variable within any given family. The sites of mutation affected the severity of disease with patients with EXT1 mutations having a significantly worse condition than those with EXT2 mutations in three of five parameters of severity (stature	Relatively few sarcomas developed; authors were unable to construct a prognostic model. Length of follow up was not reported Researchers collecting the clinical data were blind to the genotype data and vice versa.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					(X2=7.10, p<0.01), deformity (z=3.5, p<0.01) and functional (z=2.5, p=0.012) parameters). A single sarcoma developed in an EXT2 mutation carrier, compared with seven in EXT1 mutation carriers. There was no evidence that sarcomas arose more commonly in families in whom the disease was more severe. Authors' conclusions: The sarcoma risk in HME (especially in EXT1 carriers) is similar to the risk of breast cancer in an older population subjected to breast-screening, suggesting that a role for regular screening in patients with HME is justifiable.		

Improving knowledge

The questions

a) Do clinical trials improve outcomes in people with sarcoma?

b) Is the outcome for people with sarcoma improved by the use of national cancer datasets and disease-based cancer registries?

Nature of the evidence

a) Do clinical trials improve outcomes in people with sarcoma?

A US observational study of good quality (Link *et al.* 1986) compared the outcome of patients in a clinical trial of adjuvant chemotherapy for osteosarcoma with eligible patients who did not enter the trial. The UK bone tumour cohort study (Stiller *et al.* 2000) examined entry into clinical trials as a prognostic factor in people with Ewing's sarcoma or osteosarcoma.

Two observational studies of good quality, one German (Paulussen *et al.* 2003) and the other from the UK (Stiller 1988), discussed the effect of adherence to chemotherapy trial protocols and outcomes in people with bone sarcoma.

A good quality systematic review of clinical trial effects in general (Vist *et al.* 2004) was included; this study reported data from 55 studies 28 of which were oncology trials.

b) Is the outcome for people with sarcoma improved by the use of national cancer datasets and disease-based cancer registries?

Two review articles from the Scandinavian Sarcoma Group (SSG) discussed the SSG register (Bauer *et al.* 2004) (see table 11.b) and the epidemiology of STS (Olsson 2004). The SSG register collects information from all treatment centres in Finland, Norway and Sweden.

Observational studies, from the UK (Barlow & Newman 1994) and Switzerland (Remagen 1992) reported diagnostic disagreement following central review of histopathology by specialist bone tumour registry pathologists. A UK bone tumour cohort study (Stiller *et al.* 2000) compared the diagnosis recorded in disease

based registries with that in the NHS cancer registry. An unpublished study in the South West region of England (Poirier *et al.* 2004) compared people with newly diagnosed STS recorded in the cancer registry in 2003 with those identified in histopathology department clinical audits.

Summary of the supporting evidence for the recommendations

a) Do clinical trials improve outcomes in patients with sarcoma?

There is some evidence that inclusion in a clinical trial is associated with better outcome in people with bone sarcoma. It is difficult to say whether inclusion in the trial itself improves outcomes (by strict adherence to treatment protocols for example), or whether the centres that enrol patients in trials are also those that provide better care. It is also possible that trial entry criteria may exclude those patients with poor prognosis.

The UK bone tumour cohort study (Stiller *et al.* 2000) found entry into clinical trials a positive prognostic factor in people with Ewing's sarcoma but not in those with osteosarcoma.

Two studies reported better survival in people with bone sarcoma (Paulussen *et al.* 2003; Stiller 1988) or childhood rhabdomyosarcoma (Stiller 1988) treated in paediatric oncology units. The authors speculated that strict adherence to trial protocols in the paediatric centres contributed to improved survival. In both studies, centres which enrolled patients into trials tended to treat more patients than other institutions and it is difficult to separate the benefits of entry into clinical trials from those due to specialisation or case volume.

When treatment effects and selection bias are taken into account, however, there appears to be little evidence of trial effects. The systematic review of Vist and co-workers (Vist *et al.* 2004) did not find evidence of the trial effect in randomised controlled trials of therapies. The study of Link and co-workers (Link *et al.* 1986) reported similar outcomes in patients in a clinical trial of adjuvant chemotherapy for osteosarcoma and in eligible patients not enrolled but receiving equivalent treatment at the same institution.

b) Is the outcome for people with sarcoma improved by the use of national cancer datasets or disease-based cancer registries?

There was little direct evidence to answer this question. The Scandinavian Sarcoma Group register provides an example of the benefits of a national disease based register of soft tissue and bone tumours. It allows evolving treatment patterns and patient outcomes to be monitored and enables regular audit of patient management against recommendations (Bauer *et al.* 2004).

A review of the epidemiology of sarcoma (Olsson 2004) underlined the usefulness of national cancer registries. Such sources have been used to monitor disease incidence and to identify genetic and environmental risk factors for sarcoma.

Observational evidence suggests diagnostic accuracy may be improved by the central pathology review that follows the submission of a case to a sarcoma specific registry (Barlow & Newman 1994; Remagen 1992). The UK study of patterns of care for people with bone tumours (Stiller *et al.* 2000) found the bone tumour registers (with pathology review) more accurate than the cancer registries, possibly because patient information in the disease based registries was updated more often. The South West of England cancer registry study (Poirier *et al.* 2004) reported 88% concordance between diagnoses of STS in the registry and those identified from histopathological clinical audit data. Authors suggested that if quality of data sent to cancer registries could be improved, a separate sarcoma registry would not be needed.

Table 11.a Do clinical trials improve outcomes in people with sarcoma?

Abbreviations: CI, confidence interval; EFS, event free survival; MRC, Medical Research Council; NCRT, National Registry of Childhood Tumours; RCT, randomised controlled trial; RR, relative risk; SE, standard error; UKCCSG, United Kingdom Children's Cancer Study Group.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Paulussen *et al.* (2003)	To investigate why age is an adverse prognostic factor in Ewing's sarcoma.	Retrospective case series.	1426 patients with Ewing's sarcoma enrolled on one of 3 clinical trials of chemotherapy: CESS81, CESS86 and EICESS92. Median patient age was 15 years (range <1 to 54 years). GERMANY	Event free survival (EFS).	Ten year EFS 50% for patients = 15 years compared to 35% for patients >15 years. For patients older than 15: 10 year EFS was 49% in paediatric oncology units compared to 29% for other institutions (p<0.01). For patients younger than 15 years: 10 year EFS was 51% in paediatric oncology units compared to 34% in other units (p<0.01). In multivariate analysis both older age at diagnosis (>15 years, RR 1.21, p=0.05) and treatment outside a paediatric oncology centre (RR 1.34, p=0.01) were independent adverse prognostic factors. Paediatric oncology units tended to treat more patients (average 12 patients per unit compared to 4 per unit for other institutions). A greater proportion of patients treated outside paediatric oncology units had tumour volume >100 ml (73.3% vs. 65%, p=0.024). Authors' conclusions: Poorer outcome of Ewing's sarcoma patients cannot be attributed solely to biological factors, as treatment in paediatric oncology units increases survival in all age groups. It may be speculated that close adherence to the "paediatric-type" Ewing's tumour protocol	Other prognostic factors (disease stage, tumour site and volume) were incorporated into the multivariate model.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					guidelines in paediatric units may have contributed to this observation. Hence treatment following such protocols is encouraged.		

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Stiller (1988)	To compare survival rates of UKCCSG and non-UKCCSG patients with 8 of the principal types of childhood neoplasm.	Case series.	Patients (n=3115) aged 14 or less entered onto the CCRG or UKCCSG registries between 1977–1984. Patients had one of eight of the principal types of childhood neoplasm. Patients entered onto the UKCCSG register were managed at paediatric oncology centres. UK	Overall actuarial survival curves, and 3 year survival rate.	Log rank tests were used to compare the survival curves of patients grouped by diagnosis, by year of diagnosis (1977–1980 vs. 1981–1984) and by treatment centre (paediatric oncology centres vs. other teaching hospitals vs. other non-teaching hospitals). Osteosarcoma For the period 1977–1980 there was similar survival in all types of treatment centre, with 3 year survival of around 36% and 5 year survival of about 30%. For the period of 1981–1984 children treated at paediatric oncology centres showed a considerable improvement in survival (approximate 3 year survival 55%, 5 year survival 50%). Ewing's sarcoma A greater proportion of children survived at paediatric oncology centres. For 1981–1984 3 year survival at paediatric oncology centres was 50%, at other teaching hospitals 33% and at non-teaching hospitals 45% ($p<0.05$, log rank test). Rhabdomyosarcoma There was a higher proportion of survivors at paediatric oncology centres. For 1981–1984 3 year survival at paediatric oncology centres was 63%, and at other teaching hospitals 36% (insufficient data from non-teaching hospitals) ($p<0.01$, log rank test). Results were also presented for Hodgkin's disease, non-Hodgkin's lymphoma, Wilm's tumour, neuroblastoma and acute non-lymphoblastic leukaemia (but not included in this appraisal). Author's conclusions: Children with cancer should be referred to specialist centres so that they may benefit as early as possible from the latest advances in treatment.	Possibly outdated study. Not all statistical comparisons are reported. Author notes that paediatric oncology centres treated a greater proportion of Ewing's sarcoma patients with poor prognosis. Findings were unchanged when patients surviving less than 1 month were excluded. Untreated patients were excluded from the survival analysis. Follow up was shorter for the 1981–1984 group.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Link *et al.* (1986)	To determine whether multi-agent adjuvant chemotherapy improves the chances of relapse free survival in patients with non-metastatic osteosarcoma.	Main study was RCT. Comparison between outcomes of randomised and non-randomised patients was case series.	113 patients with high-grade osteosarcoma of the extremity, age <30 years, no metastases, complete surgical excision with pathological confirmation of tumour-free margins, no history of cancer or previous therapy. USA	2 year relapse free survival. Overall survival.	113 patients were eligible for entry into the trial, 36 accepted randomisation and 77 declined. All patients received surgery (either amputation or resection). In the patients entering the trial 18 received adjuvant multi-agent chemotherapy, and 18 observation only. In patients who declined randomisation, 59 elected to receive the multi-agent chemotherapy and 18 observation. Maximum follow up was 3.5 years, median follow up was 2 years. 2 year relapse free survival rate (±SE) for patients receiving adjuvant chemotherapy (trial vs. non-trial participants): 66%±13% vs. 67%±9% 2 year relapse free survival rate (±SE) for patients receiving observation only (trial vs. non-trial participants): 17%±9% vs. 9%±9% Overall survival: Using the log rank test no significant difference between the overall survival of treatment groups or trial vs. non-trial patients was observed Authors' conclusions: From the results of this study the favourable effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity appears incontrovertible.	Clinical features (age, sex, tumour site and surgery) appeared similar in those accepting and those declining randomisation. There was no formal case mix adjustment. Follow up (median of 2 years) could have been too short to demonstrate survival differences. Nearly all those treated with observation alone who experienced recurrence received both chemotherapy and surgery for their relapse. Most patients in the study received chemotherapy at some point.	3+
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	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 20,380 treated outside	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		2++

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
	compared, and any differences between patients who participated and those who did not.		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).		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 (including surgery and chemotherapy), for different clinical areas (oncology, cardiology and others) and for the different reasons patients refused to participate in the RCT (such as treatment preferences). 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.		

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Stiller *et al.* (2000)	To calculate population based survival rates for osteosarcoma and Ewing's sarcoma among patients younger than 40 years, and to identify prognostic factors related to patterns of care.	Retrospective cohort study.	2843 people with malignant bone tumours diagnosed at age 0–39 years in the UK, 1980–1994. Patients were identified through the NCRT, English regional cancer registries and Scottish and Welsh national cancer registries. The UKCCSG and specialist bone tumour registries were also checked. Lists of patients entered in osteosarcoma and Ewing's sarcoma trials were supplied by the MRC cancer trials office and the UKCCSG. UK	Overall survival.	Multivariate survival analyses (Cox proportional hazards analysis) were carried out separately for patients with osteosarcoma (n=1297) and Ewing's sarcoma of bone (n=831). Variables included in the analysis: sex, age, tumour site, year of diagnosis, entry in clinical trial and treatment centre type. Osteosarcoma RR (95% CI): • Trial 1 (reference) • non-Trial 1.01 (0.82–1.24) Ewing's sarcoma RR (95% CI): • Trial 1 (reference) • non-Trial 1.32 (1.06–1.65) Authors' conclusions: Survival from Ewing's sarcoma might be expected to improved if more patients were entered in multi-centre trials.	Only a subset of the results are presented in this appraisal, see other evidence tables. A significant positive effect of "entry into trial" was seen for Ewing's sarcoma but not for osteosarcoma. Disease stage not included as a prognostic factor. Unclear whether those entered onto trials had better prognosis to start with.	2+

Table 11.b Is outcome for people with sarcoma improved by the use of national cancer datasets and disease-based cancer registries?

Abbreviations: MRC, Medical Research Council; NCRT, National Registry of Childhood Tumours; SSG, Scandianvian Sarcoma Group; STS, soft tissue sarcoma; UKCCSG, United Kingdom Children's Cancer Study Group.

Study	*Aims*	*Design*	*Population*	*Outcomes*	*Results*	*Comments*	*Level*
Bauer *et al.* (2004)	General discussion of the SSG Register.	Review article presenting data from population based case series.	SSG Register of patients treated for bone and soft tissue sarcoma between 1986 and 2001. FINLAND, NORWAY, SWEDEN	Size, depth and grade of STS. Local control and patient survival.	In the SSG register as a whole size, depth and grade of reported STS lesions have not changed greatly over the period 1986–2001. Authors suggest that on the whole good referral practices were already established by 1986. The rate of primary referral before surgery improved from 69% in 1986–1989 to 84% in 1999–2001.	The paper lists the participating centres and number of patients reported and reviews some of the research findings emanating from the SSG. The SSG register is population based (except for FINLAND). Data not analysed statistically. In one institution, better referral practices were associated with an improvement in patient metastasis free survival	3-
Stiller *et al.* (2000)	To calculate population based survival rates for osteosarcoma and Ewing's sarcoma among patients younger than 40 years, and to identify prognostic factors related to patterns of care.	Retrospective cohort study.	2843 people with primary malignant bone tumours diagnosed at age 0–39 years in the UK, 1980–1994. Patients were identified through the NCRT, English regional cancer registries and Scottish and Welsh national cancer registries. The UKCCSG and specialist bone tumour registries were also checked. Lists of patients entered in osteosarcoma and Ewing's sarcoma trials were supplied by the MRC cancer trials office and the UKCCSG. UK	Diagnostic agreement.	Diagnoses provided by the specialist bone tumour registers and from clinical trials were based on central pathology review, as were those from the northern region young persons' malignant disease registry. 1317/2843 (46%) of patients had such a review diagnosis. These review diagnoses were compared to those entered into the English regional and national Scottish/Welsh cancer registries. Diagnoses concurred in 88% of cases. The error rate was therefore 12% at most. Authors suggest that some of the inaccuracy could be due to failure to update the cancer registry when new information became available. The most common sort of difference was the cancer registry having a less specific diagnosis than the review source.	Only a subset of the results is presented in this appraisal.	2+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Barlow & Newman (1994)	To review the contents of the Leeds Regional Bone Tumour Registry with regard to the shoulder.	Within group comparison.	145 primary bone tumours of the shoulder region in a registry of 2039 cases gathered from 1958–1994. 73 cases were malignant and 72 benign. UK	Tumour site and type, diagnostic accuracy.	Tumour site: Seventy-five per cent of tumours occurred in the proximal humerus, 20% in the scapula and 5% in the outer half of the clavicle. Tumour type: 73 cases were malignant and 72 benign. Commonest tumour types were: unicameral cyst 40 cases, osteosarcoma 26 cases and chondrosarcoma 21 cases. Simple bone cyst was the commonest diagnosis in children, chondrosarcoma in the middle age group and osteosarcoma in the over 60s. Diagnostic accuracy: Cases submitted to the register were subject to central diagnostic review. In 13 cases the preoperative diagnosis was deemed incorrect and resulted in suboptimal management. A biopsy was performed before surgery in 82/145 (57%) cases. In the remaining 63/145 (43%) patients treatment was undertaken on the basis of clinical findings alone. In 11/145 (8%) of cases the histological diagnosis of the tumour registry differed from the referring pathologist's diagnosis with important clinical implications. In 6/145 (4%) patients diagnosis was delayed by failure to order a radiological examination. In 7/145 (5%) patients diagnosis was delayed by failure to take an adequate biopsy. Authors' conclusions: An adequate biopsy specimen obtained at the time of presentation should be referred to a specialist pathologist or tumour panel for optimal management. Increased awareness of the causes of local symptoms, prompt radiological investigation and expeditious biopsy of suspicious lesions are basic prerequisites for the satisfactory management of these patients.	Some cases could date back to 1958.	3+

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
Olsson (2004)	To review epidemiological studies of STS published between 1997–2002.	Review article.			Author discusses incidence data and then genetic factors, childhood sarcoma, occupational factors, constitutional factors and other medical conditions as risk factors for STS. Author's conclusions: Several possible risk factors need to be further assessed in STS such as herbicide exposure, constitutional and hormonal factors during childhood, puberty and adulthood.		4
Poirier *et al.* (2004)	To crosscheck cancer registry data against clinical audit data.	Observational study.	Patients with STS diagnosed in 2003 in the South West region of England. UK	Concordance between diagnoses in the cancer registry and histopathology departmental audits.	ICD10 codes (C47, C48, C49, C381 and C382) and morphology codes based on WHO classification were used to extract potential cases of STS from the cancer registry. The list of cases was compared with data received from regional histopathology departments used for audit. 233 cases were coded as C49, a further 47 cases were coded as C47, C48, C381 or C382. Morphology codes identified a further 142 cases. An 88% match was obtained between the registry and audit data. Authors' conclusions: Despite the complexity of the STS anatomical presentation, it is possible to identify most cases of sarcoma on the registry using a combination of site and morphology codes. A separate national sarcoma register may be unnecessary if the quality of the data sent to cancer registries can be improved.	Unpublished abstract. The accuracy of the histopathology audit data (the implied gold standard) is unknown. It is unclear whether cases not identified in the registry search, but who were in the histopathology audit, were also included in the analysis.	3-
Remagen (1992)	To review the diagnostic accuracy of cases referred to the Swiss Society of Pathology Bone Tumour Registry.	Within group comparison.	4500 bone tumours excluding the skull. 1500 cases were referred from the Basel region and 3000 referred from elsewhere (including other countries). SWITZERLAND	Diagnostic agreement.	There was disagreement in diagnosis in 1100/4500 (24%) cases. 106/4500 (2%) of diagnoses were changed from malignant to benign. 124/4500 tumour diagnoses (3%) were changed from benign to malignant. In the remainder of cases the histological tumour type was revised.	German language paper, results extracted from English abstract.	3-

Study	Aims	Design	Population	Outcomes	Results	Comments	Level
					Author's conclusions: It is important that close collaboration is established between clinician, radiologist and pathologist to produce the correct diagnosis and deliver appropriate treatment.		

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Appendix A. Search strategy

Medline, Embase (a modified search strategy with different index terms was used for Embase) and the Cochrane Library were searched as core databases – Cinahl, British Nursing Index, Psychinfo and Amed were searched if relevant to the subject of the search.

The basic search strategy is shown below, using Medline syntax. This strategy was combined with further terms relevant to each research question.

1. exp "Neoplasms, Connective and Soft Tissue"/
2. sarcoma$.tw.
3. Sarcoma, Alveolar Soft Part/
4. exp Myosarcoma/
5. myosarcoma$.tw.
6. rhabdomyosarcoma$.tw.
7. angiosarcoma$.tw.
8. (hemangiosarcoma$ or haemangiosarcoma$).tw.
9. lymphangiosarcoma$.tw.
10. (stewart-treves adj (tumo?r$ or sarcoma$ or syndrome)).tw.
11. (hemangiopericytoma$ or haemangiopericytoma$).tw.
12. adenosarcoma$.tw.
13. cystosarcoma$.tw.
14. phyllodes.tw.
15. fibroadenoma$.tw.
16. dermatofibrosarcoma$.tw.

17. fibrosarcoma$.tw.

18. gastrointestinal stromal tumo?r$.tw.

19. GIST.tw.

20. leiomyosarcoma$.tw.

21. liposarcoma$.tw.

22. malignan$ fibrous histiocytoma$.tw.

23. MFH.tw.

24. malignan$ peripheral nerve sheath tumo?r$.tw.

25. MPNST.tw.

26. myxosarcoma$.tw.

27. neurofibrosarcoma$.tw.

28. synovioma$.tw.

29. adamantinoma$.tw.

30. ewing$.tw.

31. primitive neuroectodermal tumo?r$.tw.

32. PNET$1.tw.

33. chondrosarcoma$.tw.

34. mesenchymoma$.tw.

35. osteoclastoma$.tw.

36. osteosarcoma$.tw.

37. malignan$ giant cell tumo?r$.tw.

38. sarcoma$.jw.

39. (chordoma adj sacrum).tw.

40. (retroperitoneal adj sarcoma$).tw.

41. (dermatofibrosarcoma protuberan$ or DFSP$1).tw.

42. uterine sarcoma$.tw.

43. (mullerian adenosarcom$ or malignant mullerian mixed tumo?r$ or MMMT or malignant mesoderm$ mixed tumo?r$).tw.

44. (endometrial stromal sarcoma$ or endometrial stromal tumo?r$).tw.

45. metaplastic carcin$.tw.

46. carcinosarcoma$.tw.

47. (ovarian sarcoma$ or vulva$ sarcoma$).tw.

48. gyn?ecolog$ sarcoma$.tw.

49. or/1-48

Appendix B. Position paper: prosthetic rehabilitation of the post tumour amputee

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a) Introduction/Patient pathway

Despite great progress in medicine and technology, the basic considerations with regard to amputation and prosthetics remain constant. The disability increases with each more proximal level of amputation, particularly with the loss of major joints. Amputation is a challenge, not only to patients, their families, but also the surgeon, the entire prosthetic team and clinicians.

The latest amputee statistical database for the United Kingdom – 2003/2004 Report by the National Amputee Statistical database team indicates that overall in the United Kingdom, amputations referrals due to all inclusive causes for the years 2003/2004 were noted to be 5210.(1). Overall lower limb amputations (LLA) account for 92% (n= 4769), of which 3% (n= 121) had tumour related amputations.

In the case of Upper limb amputation (ULA), overall they account for 6% (n=311), of which 14% (n=43) had tumour related amputation. There was a notable increase in the referrals due to primary malignancy in ULA from 7% in 2002/03 to 13% in 2003/04.

Table. Neoplasia/tumour related amputations for 2003/2004 (out of a total of 5210 patients)

Neoplasia related amputations	***Malignant primary***	***Malignant secondary***	***No details***
164 patients	125 patients (76%)	7 patients (4%)	32 patients (20%)

Hence the majority of the tumour related amputations were in malignant primary tumours.

Though post tumour amputee population only make up 3% of the entire cohort, because they are in the younger active age group, they quite rightfully pose major demands on prosthetic rehabilitation services. As a majority of these amputees are under the age of 65, their prosthetic rehabilitation aims are not just achievement of independent mobility, but returning to work and their previous, or new hobbies/leisure pursuits.

The odds are stacked against these patients, as unfortunately because of tumour presentation, they do necessitate high proximal amputations unlike in the trauma cohort. A majority of the post tumour lower limb amputees are usually either transfemoral (above knee) amputees or at hip disarticulation level / hemi-pelvectomy level, in sarcoma related cases in order to achieve sufficient clearance. In the upper limb, the proximal amputations are at, forequarter, shoulder disarticulation or transhumeral (Above Elbow) levels.

More proximal the amputation in the limb, the increased inherent difficulty of achieving near normal status and physical independence, regards mobility and activities of daily living.

Amputee/prosthetic rehabilitation in the United Kingdom is a sub speciality within the remit of rehabilitation medicine and most of the services are run via specialist Disablement Services Centres (DSC) in individual National Health Service Trusts across the country. Currently there are 44 DSC's in the United Kingdom.

The British Society of Rehabilitation Medicine report (BSRM) of Oct. 2003 outlined the standards and guidelines for amputee and prosthetic rehabilitation.

The report put forward a template for Prosthetic and Amputee Rehabilitation Centres (PARC), at Tertiary level, local level and at a limited lower limb PARC level. (2)

Generally about one third of the 44 DSCs in the UK (approximately 14 DSC's) are large enough to cope with all the intricacies of comprehensive prosthetic/amputee rehabilitation. Hence two thirds of the DSCs are unable to cater for all the needs of the amputees.

The areas where they have difficulty in providing service provision are inability to manage paediatric patient and some DSC's are unable to provide upper limb prosthetic services. Some DSC's are unable to provide extremely proximal complicated modular prosthesis, namely for either a hemi-pelvectomy or a fore quarter amputation. Additionally some centres are unable to provide services for patients who need myoelectric prosthetic technology in the upper limb amputee.

b) Referral pattern:

Currently the patients with limb amputations are referred from various oncology units/hospitals to their local Disablement Services Centres. These 44 Disablement Services Centre are usually Supra-District Centres as indicated above and about 14 such centres are on a sub-regional to regional basis and hence get referrals from a large number of district health authorities. If the particular DSC were unable to manage the post tumour amputee then appropriate pathway would be to refer to a larger DSC or a designated specialist centre for the ongoing amputee rehabilitation.

c) Current delivery of care:

Depending on where the tumour related amputation has been performed, referral is sent to the local DSC. Patient is assessed by the DSC multidisciplinary team (in majority of the cases) and the team embarks on a prosthetic rehabilitation programme.

For example, in an above knee amputee (transfemoral), once the stump is healed and settled as regards oedema, then in consultation with the prosthetic team, an appropriate modular lower limb prescription is recommended and the patient is

followed up for fitting and delivery of the prosthesis. The patient then undergoes gait retraining with regular physiotherapy follow up. Patients initially start with trial in the parallel bars in the physiotherapy department followed up by assisted walking, either with crutches or two sticks, followed up by moving onto walking with one stick and eventually without any walking aids. The patient is followed up by the prosthetist to accommodate any volume changes of the stump, which necessitate appropriate socket adjustments or replacements. As most of these patients are from a younger age group, these patients go onto modular lower limb prosthesis with a free knee mechanism to try and simulate near normal gait pattern in majority of cases. Caveat in this case is that majority (58%) of unilateral amputees do sustain falls hence only after appropriate assessment gait retraining, any independent ambulation is considered (3).

As the stump volume changes quite significantly in the first three months, the patient is followed up on a 4 to 6 weekly basis initially, to accommodate stump changes and in most cases a refit of the socket is necessitated by about 3 months time. Once the patient achieves full usage of the prosthesis and independent mobility, then in order to keep up with the increasing demands a duplicate modular prosthesis is prescribed. All amputees need lifelong follow up via the amputee/prosthetic rehabilitation services.

d) Accepted best practice:

As tumour related amputations make up only 3% of the overall yearly amputee cases, logically it beholds us to try and concentrate the entire care package of, assessment, review and follow up of these patients at specialist Tertiary PARC centres on an ‘one stop centre’ basis, rather than referral to local Disablement Services Centres. Tumour related amputee patients are usually in the younger age spectrum and 64% of the patients are below the age of 65 and in a significant number of cases, return back to work, albeit with changed work patterns. The majority of these patients are lower limb amputees and as noted earlier, unfortunately have high proximal level amputations. Most of these patients aspire to achieve in addition to independent mobility, pursuit of their hobbies. These are low volume and high demand group of patients.

e) Recommended best practice regime would be:

1. Assessment of the patient with limb tumour at sub-regional, regional oncology unit.

2. Referral for pre-amputation assessment by the oncology unit to a specialist Disablement Services Centre – Tertiary PARC with a comprehensive multidisciplinary team - currently approximately 14 such centres in the UK.

3. Pre-amputation assessment and counselling of these patients at the Tertiary PARC.

4. Patients given the option of meeting with an age and sex matched established amputee.

5. Meeting up with all the multidisciplinary team members inclusive of the prosthetic team, who would look after the patient post amputation.

6. Liaison with the referring Oncology Unit by the Consultant in Rehabilitation Medicine, as to the most appropriate level of either bone resection or disarticulation and a myoplastic closure if feasible. Advice the referring team as to post amputation pain and stump management. Avoidance of bandaging after removal of sutures and introduction of stump shrinking juzo socks after removal of sutures. Oncology surgical team to establish close liaison with the physiotherapy and occupational therapist locally, to try and assist with immediate post amputation mobilisation, albeit initially with elbow crutches or Zimmer frame. Particular advice as to avoidance of falls to be re-iterated.

7. Review by the Tertiary PARC team within 4 to 6 weeks post amputation surgery and start of amputee/prosthetic rehabilitation programme.

8. Introduction of modular prosthesis with Total Contact sockets with appropriate siliconised liners, modular joint units and modular feet.

9. Multidisciplinary team to follow patient up closely during fitting and delivery and to organise initial gait re-training centre in the specialist Tertiary PARC physiotherapy department.

10. Once the patient has achieved, safe albeit assisted mobility, then the ongoing gait re-training/physiotherapy is to be organised at a local level near the patient's home.

11. Patient to be followed up by the Consultant led team for ongoing review of the stump, to screen for any local recurrences in residual stump and establish close liaison with the surgical oncology team, as well on the oncology treatment centres.

12. To provide advice regards surviving limb.

13. Lifelong follow up by the Tertiary PARC team.

f) Contentious issues:

1. Specialisation.

Amputee/prosthetic rehabilitation is a sub-speciality in the remit of Rehabilitation Medicine within the Royal College of Physicians (RCP). The minimum requirements for a specialist registrar with Certificate of completion of specialist training, is that the person should have completed 15 months of amputee/prosthetic rehabilitation training, prior to being allowed to be able to do independent prosthetic clinics at a consultant level.

Currently there are only a limited number of Consultants in Rehabilitation Medicine who have requisite expertise and training to do independent amputee/prosthetic clinics. A number of these Consultants are now retiring and because of lack of appropriately trained specialist registrars, it is becoming more apparent that a number of new Consultants are being partly forced into doing these specialist clinics, albeit without the requisite training, knowledge and experience. The Specialist Advisory Committee of the RCP and the British Society Rehabilitation Medicine is addressing these issues.

Additionally it is disappointing that increasing number of individual Trusts, are managing these specialist amputee/prosthetic services at sub-Consultant level contrary to BSRM / RCP and Clinical Governance recommendations.

2. Potential resource implications:

With the ever advancing field of prosthetic technology, private prosthetic companies are increasingly introducing advanced technological items, namely in the nature of updated knee joint units, updated prosthetic feet, updated silicone high definition cosmesis etc. These expensive individual modular items obviously generate high costs for the local Disablement Services Centres and hence cause major budgetary impositions. As to the high definition silicone cosmesis, recently the government has allocated, limited funding over the last two years to individual DSC's to try and kick start supply of these expensive silicone cosmeses. Some DSCs have drawn up guidelines and waiting lists for prescriptions of silicone cosmesis, for equitable provision of these high cost items.

3. Staffing level issues:

It is paramount that, a Consultant led multidisciplinary team assesses patients. Apart from Tertiary PARC's, the rest of the centres do have gaps in service delivery. These gaps relate to insufficient number of sessions that the Consultant is able to provide for amputee rehabilitation service delivery, insufficient numbers in the multidisciplinary team with shortage of therapy staff, therapy facilities, counselling staff, skilled nursing staff and appropriately trained prosthetic staff to cope with proximal amputations or upper limb amputees.

g) Proposed changes to the current situation:

Strongly recommend that the recommended best practice protocol detailed in earlier section should be followed for post tumour related amputee rehabilitation. Patient to be seen at specialist Disablement Services Centre – Tertiary PARC's for ongoing lifelong follow up with regular feedback / liaison with the oncology teams.

h) Key commissioning recommendations:

1. PCTs / Trusts to agree funding and facilitate the process, for all post tumour amputations be done at regional oncology units in close liaison with Tertiary PARCs.

2. Commissioners to facilitate post tumour amputee referrals to specialist DSC's – Tertiary PARCs – one stop centre, with appropriate funding mechanism for these, low volume, high cost patients.

3. Commissioners to assist with appropriate funding mechanisms for introduction of new prosthetic technology items, as they become available in order assist with improving the rehabilitation potential of these deserving patients via the specialist DSC's – Tertiary PARC.

4. Commissioners to assist with regional and national data collection of these patients with organised regional and national audit programmes.

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Appendix C. Position paper: gastrointestinal stromal tumours: diagnosis, staging and a surgical treatment pathway

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a) Epidemiology

Mesodermal tumours of the gastrointestinal tract are rare and their classification and our belief about their histogenesis have altered over the last 60 or so years since their original descriptions as a surgical entity in the 1940's.

Initially on light microscopy they were all considered to be of smooth muscle origin and later the electron microscope showed us that a few but not most of the tumours showed good features of smooth muscle ultrastructure. Some showed features more like neuronal tissue and some showed neither or both. The application in the 1980's of immunohistocytochemical classification allowed these mesodermal or stromal tumours to be separated into smooth muscle types, neurogenic and non-specified types based on the selective expression of smooth muscle or neurogenic surface antigens but collectively referred to as stromal tumours (Mazur & Clark, 1983).

The discovery that a large number of these stromal tumours over express CD117 the protein product of the KIT oncogene has allowed a further clarification of the pathology and now we regard the term gastrointestinal stromal tumour as being applied only to those intra-abdominal mesodermal tumours showing the presence of CD117 and positivity (with a few exceptions) is a requirement for diagnosis of GIST. The most likely candidate cell of origin is the gastrointestinal tract pacemaker cell of Cajal (Sircar et al 1999). Exceptions to an absolute requirement to express CD117 to secure a diagnosis of GIST might occur for

example where the ultrastructural features are met and the tissue appears immunologically inert such tumours could be called stromal tumour consistent with GIST. Otherwise, the presence of CD117 positivity is a requirement to be labelled GIST. GISTs may additionally express other mesodermal markers such as CD34 and smooth muscle actin (SMA) but these are not diagnostic nor exclusion criteria.

Stromal tumours not expressing CD117 and having the appropriate ultrastructural and immunohistochemical features of smooth muscle or neurogenic differentiation should be labelled leiomyosarcoma or schwannoma as appropriate but even combined are the minority of the whole of intra-abdominal mesodermal tumours.

The overall incidence of GIST is thought to be between 10–20 per million of population based on European data and this seems consistent with SEER data from the US. In the UK one might expect to see about 500–1000 cases per annum and account for ~1% of all gastrointestinal tract malignancies. It is likely that the true incidence is higher as smaller lesions are likely to be asymptomatic and thus escape detection and reporting.

There is an equal male: female ratio and the dominant age range is 50–60 years. GIST's are rare before age 40 years and certainly very rare in children but not unheard of.

No specific risk factors are known except for the increased incidence in the rare Carney's syndrome of pulmonary chondromata, gastrointestinal stromal tumours and non-functioning extra-adrenal para-gangliomas; such patients are usually female and so far the world-wide literature reports only about 100 cases. In such cases the behaviour of the tumours seems very indolent (Carney JA, 1999).

b) Clinical presentation

GIST can occur at any site in the gastrointestinal tract and the specific symptoms relate to the anatomic site and the local effects. The site distribution shows a dominance for the stomach 60%, small bowel sites 25%, large bowel 10%, oesophagus ~5% and extra-lumenal sites such as omentum, mesentery and peritoneum accounting for <1% (Emory et al 1999, DeMatteo et al 2000). Since

tumours of the small intestine are rare GIST's represent about 1/3 of all malignancy in the small intestine.

In the oesophagus the symptoms are related to dysphagia and occasionally bleeding. In the stomach symptoms most often relate to early satiety, epigastric fullness, dyspepsia or upper GI haemorrhage from ulceration of the overlying mucosa.

Small bowel GIST usually present with mass in the abdomen, unexplained blood loss or colicy abdominal pains. Large bowel GIST present in the same way as epithelial large bowel tumours with symptoms of alteration in bowel habit, bleeding, and mass effect especially in the rectum. Other times, in about 10% of cases, symptoms are not manifest until the tumour is of a considerable size perhaps >20cm when symptoms from systemic disturbance such as anorexia, fever, weight loss, ascites or other features of advanced disease may occur (Pidhorecky et al. 2000)

c) Diagnostic strategies

Diagnosis and the method of diagnosis will be largely directed by the clinical presentation. The presentation with overt upper GI tract haemorrhage will mandate upper GI endoscopy and reveal the presence of a mucosa covered elevation of the gastric wall into the gastric lumen. In cases with bleeding the tumour is usually >3cm in diameter and a point of ulceration or 'pit' is commonly present. Smaller and perhaps incidentally discovered tumours do not have a pit or ulceration point.

Endo luminal visualisation does not usually reveal the extent of the primary as the majority are mostly extra-lumenal and so the true size can be revealed only by CT imaging or by EUS.

Rectal masses may be felt at digital examination and then visualised as mucosa covered indentation by endoscopy. Once again the true local extent is likely only to be revealed by CT/MRI of the abdomen and pelvis.

Small bowel GISTs are unlikely to be demonstrable endoscopically and might be revealed in the course of investigations of abdominal symptoms by small bowel

contrast studies or more likely at CT of the abdomen. Thus it is unlikely only larger masses in the small bowel are likely to come to diagnosis.

Endoscopic biopsy usually reveals only normal mucosa from the relevant viscus as this is to be expected as the lesion is entirely submucosal unless surface ulceration has taken place. Deep biopsy at the point of ulceration or traversing the mucosa into the underlying muscularis is possible but carries a hazard of initiating bleeding and rarely even perforation of the viscus. Thus routine biopsy of a mucosa covered lesion is not contributory to diagnosis of GIST and not necessarily a requirement of treating the lesion (Conlon et al 1995).

Endoscopic ultrasound demonstrates the lesion to arise in the muscular layer of the intestine wall and can be useful in certain situations where the lesion is small and indeterminate and discrimination between a GIST and heterotopic pancreas or bowel wall lipoma is thought necessary. In general however since most lesions except the very small <1.5cm will be considered for resection without a requirement of tissue diagnosis the value of EUS rests with obtaining tissue in a situation where resection is to be deferred to permit inclusion in a trial of neoadjuvant therapy or where non-surgical therapy is to be considered perhaps because the patient is thought too unfit to tolerate surgical intervention. EUS to determine the size of a lesion greater than 4cm in diameter is unlikely to be helpful as the range of EUS devices becomes imprecise at this depth.

On CT the lesions tend to be well defined and without evidence of clear vascular invasion or encasement (Lau et al 2004). Intra-tumoural CT characteristics of GIST usually show the lesion to be of ~30 hounsfield units and to be mostly extra-lumenal in 70% of cases. There is slight enhancement after IV contrast to ~60 hounsfield units. The enhancement is more heterogeneous in the larger tumours (Ghanem et al 2003 and Lee at al 2004). This heterogeneity in larger lesions has also been demonstrated at EUS and some experts have tried to stratify the biological behaviour of lesions on the basis of heterogeneity of echo pattern (Palazzo et al 2000). In general however this has not found universal application. EUS may be more applicable in the small (<1.5cm) homogeneous tumour where an observation strategy is to be pursued and EUS can be used to monitor the tumour size and internal texture.

Percutaneous biopsy is possible but results in seeding of tumour and should not be performed except in those patients not to be considered for surgery with curative intent such as those where medical therapy is being considered for disseminated disease or those too infirm to tolerate operation.

d) Staging

The extent of disease evaluation involves assessment of local resectability and in particular the possibility of adjacent organ invasion. In the pelvis MRI is probably superior to CT as it provides close definition of tissue planes and neurovascular structures. Abdominal and thoracic GIST's are best staged by CT scan. Occasionally if invasion into adjacent structures such as the left lobe of liver or tail of pancreas is suspected then a gastric GIST's may benefit from EUS assessment.

The main sites of dissemination are locally into the peritoneal space, the liver and invasion into adjacent organs. It is exceptional to see metastases outside of the abdomen in the absence of intra-abdominal metastases and so routine CT of the chest is not necessary but CT of the abdomen and assessment of the liver is mandatory. Adjacent organ invasion may be present and is likely to be evident on CT scan. Similarly, the presence of sarcomatosis and ascites are readily detected by CT as peritoneal deposits tend to be bulky rather than milliary.

Since lymphnode metastases are most exceptional (<0.0003%) routine assessment of the regional nodes is unnecessary (Fong et al 1993).

e) Surgical strategies and requirements

Surgery may be needed in the emergency situation for example for a ruptured or bleeding GIST. In such a situation general surgical principles to control the situation and save the patient's life should supervene over otherwise accepted strategies in the surgical therapy of GIST.

As a basic principle surgical therapy is directed to achieve complete elimination of all evaluable disease, with negative resection margins and without tumour rupture. Completeness of resection has been shown to correlate with survival (DeMatteo et al 2000, Langer et al 2003). In the past surgeons carried out

enucleation of tumours. This is not likely to achieve the desired result and as well as a high risk of local failure risks local seeding. Resection margins do not need to be large and should provide at least 1cm of macroscopically clearance from the tumour edge. The exact operation will of course depend on the individual location and size. This small GIST of the stomach for example can be adequately dealt with by wedge resection either open or laparoscopically (Kimata et al 2000) but a larger tumour will mandate either sub-total or total gastrectomy.

Since nodal disease is an exceptional and late event and if present carries a very poor prognosis there is no requirement for regional lymphadenectomy as this is at best non-contributory and may add avoidable morbidity.

Even despite meticulous surgery and resection with negative margins the patient is still at risk of local and distant failure and this hazard is determined by the individual tumour characteristics of size and mitotic rate. Risk stratification based on these criteria was agreed at the NIH consensus conference in 2001 (Fletcher CD et al 2002). Categorisation into a risk of malignant behaviour is preferable to separation into benign or malignant as it is inevitable that some small and mitotically inactive tumours will behave aggressively with early metastatic behaviour and the converse also being true.

RISK	TUMOUR SIZE	MITOTIC COUNT
Very Low Risk	<2cm	<5/50HPF
Low Risk	2–5cm	<5/50HPF
Intermediate Risk	<5cm 5–10cm	6–10/HPF <5/50HPF
High Risk	>5cm >10cm any	>5/50HPF any >10/50HPF

Low risk lesions may be followed annually as the time to recurrence is likely to be long. High risk lesions require closer scrutiny and follow up by CT scan every 3 months for the initial 24 months might be reasonable.

At the present time adjuvant therapy is not advocated routinely as there are no data to show an advantage from systemic therapy or radiation. The use of

imatinib in the adjuvant setting is currently being examined by a large intergroup trial in the US (ACOSOG Z9001) for tumours greater than 3cm diameter.

f) Management of recurrent disease

Recurrence is a common event in GIST's, affecting as much as 50% of all cases by 12 months and a greater number if one includes only the high risk cases (DeMatteo et al, 2000).

Of those patients that recur 1/3 will do so by local recurrence alone, 1/3 by distant disease (almost always to the liver) alone and 1/3 will recur by a mixture of local and distant disease. Extra-abdominal recurrence as the first site of recurrence is most exceptional. Re-operation where all evaluable disease can be removed shows a trend for improved survival and is most pronounced where the only site of recurrent disease is liver metastases and especially in cases where the disease free interval has been long. It follows that mostly these will be cases with low risk primaries (Mudan et al 2000).

Further recurrence after resection of recurrent disease is common and warrants consideration of adjuvant therapy with imatinib.

As with initially inoperable disease downsizing with imatinib as a selection tool for operation is appropriate in the trial setting.

Figure 1 below summarises the management pathway for an elective presentation of a GIST of the stomach or oesophagus. Investigations of a small bowel GIST might include barium meal and follow through instead of endoscopy while a colonic tumour will necessitate colonoscopy.

Figure 1. The management pathway for an elective presentation of a GIST of the stomach or oesophagus.

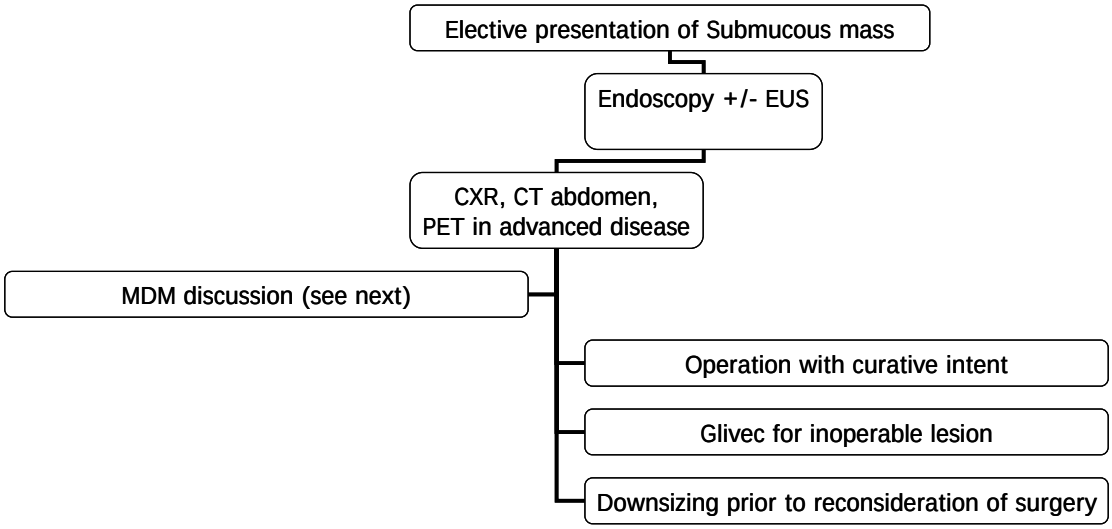
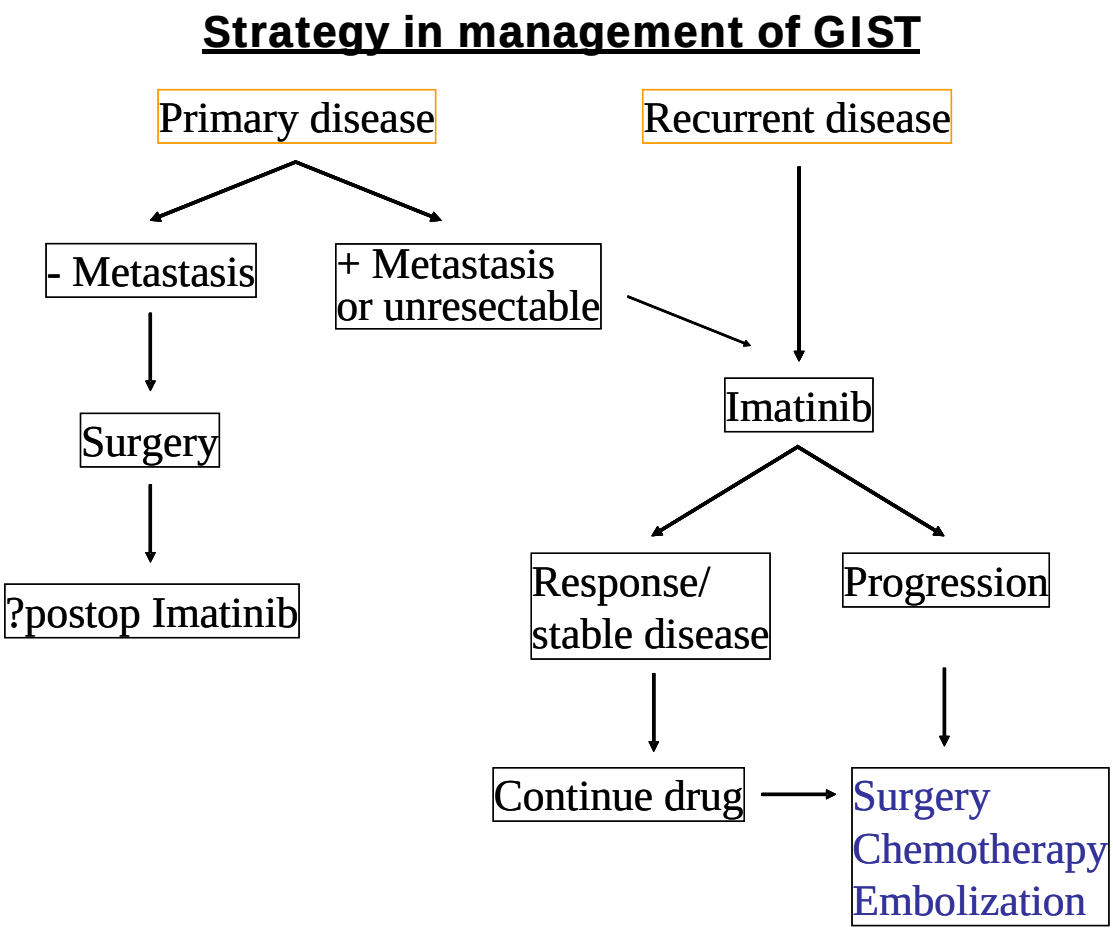


Figure 2. Strategy in the management of GIST.



As seen in figure 2, following diagnosis and staging the treatment strategy is dictated by the extent of disease and can be summarised as above to incorporate recent advances in medical oncology.

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