Clinical practice guidelines for the management of adult onset sarcoma

In collaboration with

1 Clinical practice guidelines for the management of adult onset sarcoma

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

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For more information, contact the Cancer Helpline 13 11 20

1 Foreword

1.1 Foreword

Sarcomas are rare malignant tumours of bone and soft tissue. They are a heterogeneous group of malignancies, and include many anatomical sites and subtypes. There are approximately 850 new cases of sarcoma each year in Australia.

Increasingly, new prognostic factors and therapeutic approaches for sarcoma are being identified. However, the rarity of sarcoma and its sub-types makes it challenging to determine optimal treatment strategies. In addition, there are significant gaps in the evidence base used to underpin clinical decision making for patients with sarcoma.

This project was commenced as a collaboration between the Australasian Sarcoma Study Group (ASSG) and Cancer Council Australia (CCA) in 2011. The aims of the project were to appraise the available evidence guiding the management of patients with bone and soft tissue sarcoma, with an emphasis on Australian experience, access to specialist centres and facilities.

The process has been invaluable in bringing lead clinicians managing sarcoma, across a range of disciplines, to develop common shared understanding of the current evidence and to identify key research gaps. Development of pathways of care, both state and national, is a natural sequelae to this process.

The working party were asked to decide on the questions that were most relevant to their disciplines. The selected questions reflected the gaps in knowledge that impacted most on daily management decisions. As an ab initio set of guidelines, the original scope of these guidelines was broad. The key areas covered have been refined to include:

- Diagnosis
- Multidisciplinary treatment

- Chemotherapy (Systemic therapies)
- Radiotherapy
- Surgery
- Follow-up

The Wiki Guidelines platform that was used to develop these guidelines is unique. It enables iterative, ongoing and interactive guideline development. The Wiki will facilitate monitoring and assessing literature updates and allows guideline content to be updated instantly when required. In this way, the guidelines become a 'living document' which reflect the latest evidence available.

The working party recognise that sarcomas affect children and adolescents, as well as adult members of the community. However, for reasons of pragmatism and resource, the scope of this first iteration is restricted to adult bone and soft tissue sarcoma. Gastrointestinal stromal tumours (GIST), Kaposi's sarcoma and desmoid fibromatosis were excluded. It is anticipated that next iteration of these guidelines will also include childhood, adolescent (AYA) and gynaecological sarcomas.

There were specific challenges encountered during the development of these guidelines, as low levels of evidence often underpin clinical sarcoma practice. Balanced with this is a pragmatic requirement for clinicians to make decisions on the optimal management of their individual patients. Nonetheless, these guidelines are based on a systematic review and a rigorous appraisal process, rather than a 'consensus document'.[1] A separate consumer guideline has not been developed. This decision reflects the complexity of sarcoma, as well as the availability of 'on line' consumer resources within Australia and the international community. Links to consumer resources have been provided in the "Information for consumers" section.

Sarcomas have traditionally been managed by wide excisional surgery and radiotherapy; with the use of chemotherapy reserved for advanced disease. Advances in multidisciplinary care have improved the evaluation and care of patients with this disease. In addition to paradigm shifts towards for example, limb-conserving surgery, there have been developments in other key modalities including radiotherapy techniques and novel therapeutic agents for specific tumor subtypes. Accurate pretreatment evaluation is therefore critical, particularly in planning multimodal treatment with curative intent, and also in providing 'best practice' treatment for advanced disease.

These guidelines highlight the importance of early sarcoma referral to multidisciplinary centers that specialise in treating this disease. Caseload and experience is associated with improved rates of functional limb preservation, lower rates of local recurrence, good rates of overall survival and improved quality of life.

The importance of the multidisciplinary team in initial assessment, diagnosis and making decisions about treatment is strongly endorsed by these recommendations. A multidisciplinary approach (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists, with experience in sarcoma), or within reference networks sharing expertise and treating a high number of patients annually is preferred. These centres are usually involved in ongoing clinical trials, in which sarcoma patients' enrollment is highly encouraged.

This centralised referral should be pursued as early as at the time of the clinical diagnosis of a suspected sarcoma. The importance of appropriate diagnosis, including biopsy, review by an experienced histopathologist, and determination of grade and subtype to preoperative planning –particularly preoperative radiotherapy – cannot be underestimated.

In practice, referral of all patients with a lesion likely to be a sarcoma would be recommended. This would mean referring all patients with an unexplained deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of >5 cm (or arising in childhood).

The draft guidelines containing 54 recommendations and 35 practice points were released for initial public consultation for a 30 day period on 3 September 2013. The consultation process involved soliciting public comments by sending email alerts to recipients comprising relevant professional organisations, state and territory Cancer Councils and individual clinical experts and consumer organisations in Australia and New Zealand, and inviting them to post their comment on the Cancer Council Australia Cancer Guidelines Wiki. During the public consultation phase nine public comments were received. These led to further edits, which were reviewed in detail by the working party.

We hope these guidelines will provide accessible up-to-date research for multidisciplinary sarcoma teams, individual clinicians, students and consumers. There are significant gaps in the evidence however, these are included where possible, in the form of future research questions that need to be addressed by good quality collaborative trials.

A key outcome of this process has been the need to develop more formal communications between sarcoma centres and clinicians, particularly in relation to current trials, and access.

This is the first step towards more standardised care for patients with sarcoma across the nation and provides a framework to educate the community about specialist pathways and to enhance inter-group collaboration.

I would like to thank my colleagues on the working party who gave voluntarily of their time to undertake the challenging task of appraising the evidence, writing the recommendations and meeting the guideline development deadlines. I thank the CEO of Cancer Council Australia, Professor Ian Olver for his support to this process. I also thank Cancer Council Australia's project team; without the professionalism, drive and persistence of Christine Vuletich, Jutta von Dincklage, Laura Holliday these guidelines would never have been.

Susan Neuhaus

Chair, Sarcoma Guidelines Working Party

On behalf of the Australasian Sarcoma Study Group, Cancer Council Australia and the Working Party

1.1.1 Reference

1. ↑ Clinical Guidelines Network Cancer Council Australia. *Development of Clinical Practice Guidelines using Cancer Council Australia's Cancer Guidelines Wiki. Handbook for section authors and the guideline working party.* CCA Sydney; 2014 Available from: http://wiki.cancer.org.au/australiawiki/images/9/9b/CCA_Clinical_Practice_Guideline_Development_Handbook.pdf.

2 Summary of recommendations

2.1 Summary of recommendations

This resource has been developed, reviewed or revised more than five years ago. It may no longer reflect current evidence or best practice.

For explanation of levels of evidence and grades for recommendations, see Levels of evidence and grades for recommendations below. You may also like to refer to the Appendix - Guideline Development Process

2.2 Recommendations

2.2.1 Diagnosis

2.2.2 What are the relative rates of efficacy and accuracy of various biopsy modalities in BSTTs?

Recommendation	Grade
Biopsy technique of choice is needle core biopsy (NCB) performed in a specialist sarcoma unit setting with appropriate multidisciplinary input.	**D**

Point(s)
In essence, generous numbers of needle cores of adequate length, performed with the aid of imaging, in various directions within the tumour, allows for tumour heterogeneity. In most cases this results in accurate diagnosis, grading and harvesting of adequate tissue for appropriate ancillary diagnostic techniques and, in appropriate circumstances, tissue banking. Refer to the Royal College of Pathologists of Australasia Soft Tissue Tumour Resection Structured Reporting Protocol 1st Edition (2011)

2.2.3 What are the most appropriate imaging modalities for diagnosis and staging of BSTTs?

Recommendation	Grade
Magnetic resonance imaging is the imaging modality of choice for extremity tumours.	**B**

Point(s)
CT is usually adequate for abdomino-pelvic masses.
Further imaging and biopsy only performed after review by a surgeon or other member of a sarcoma team.
CT chest be performed at diagnosis to assess for metastatic disease.
PET-CT may be used prior to radical surgery of soft tissue sarcomas.

2.2.4 What is the impact of delay in referral to a specialist centre in BSTTs?

Recommendation	Grade
Immediate referral to a specialist sarcoma unit to be sought when a tumour of bone or soft tissue (other than simple lipoma) is suspected.	**D**

Point(s)
In practice, any mass lesion greater than 5cm in size, and lesions deep to or attached to deep fascia, should be considered a sarcoma until proven otherwise.
Refer to a specialist sarcoma unit.

2.2.5 Multidisciplinary Treatment

2.2.6 What is the role of prognostic factors in management of BSTTs?

Recommendation	Grade
Statistical models assessing the influence of prognostic factors can be used to counsel patients and to stratify their need for adjuvant therapies or entry into clinical trials.	**D**

Point(s)
Accurate data collection will facilitate further study in this area. Tissue banking will allow further

Point(s)
assessment of tumours as new diagnostic and therapeutic modalities emerge.

2.2.7 What is the outcome of a second opinion in BSTT pathology?

Recommendation	Grade
Whenever a primary diagnosis of bone or soft tissue sarcoma is made outside the context of a specialist sarcoma unit, wherever possible, referral to an expert pathologist (within a specialist sarcoma unit) for review of the diagnosis and grade should be undertaken before definitive management is instituted.	**D**

2.2.8 Does referral to a specialist centre improve outcomes?

Recommendation	Grade
Patients with suspected sarcoma to be referred to a specialist sarcoma unit prior to diagnosis in order to reduce the rates of incomplete excision, reoperation, local recurrence and to improve survival.	**C**

2.2.9 Chemotherapy (systemic therapies)

2.2.10 What is the role for adjuvant systemic therapy for adults with BSTT?

Recommendation	Grade
Curative treatment of high-grade osteosarcoma comprises chemotherapy and surgery.	**B**
Pre-operative chemotherapy for high-grade osteosarcoma including cisplatin, doxorubicin and in selected patients high-dose methotrexate, improves outcomes compared to regimens omitting high-dose methotrexate.	**C**
As for osteosarcoma, doxorubicin and cisplatin are indicated for malignant fibrous histiocytoma of bone.	**D**
As for osteosarcoma, doxorubicin and cisplatin are indicated for high-grade spindle cell sarcomas of bone and malignant fibrous histiocytoma.	**D**

Recommendation	Grade
Curative treatment of Ewings sarcoma comprises of a combination of chemotherapy and surgery and/or radiotherapy.	**B**
The use of post-operative chemotherapy in adult type soft tissue sarcomas is not the current standard of care.	**D**
The use of pre-operative chemotherapy in adult type soft tissue sarcomas is not the standard of care.	**D**

Point(s)
Patients considered for chemotherapy should be referred for clinical trial participation.

2.2.11 What is the role for systemic therapy in advanced soft-tissue sarcoma?

Recommendation	Grade
There is no evidence to support combination chemotherapy regimens over sequential single agent regimens in the first-line treatment of advanced soft-tissue sarcomas.	**B**
Single agent ifosfamide can be considered as second-line treatment for patients who have not received ifosfamide as first-line.	**B**
Dacarbazine with or without gemcitabine is reasonable third-line therapy after exposure to doxorubicin and ifosfamide in advanced soft tissue sarcoma.	**B**
Systemic therapy with paclitaxel is reasonable in all patients with angiosarcoma, given the palliation that can be offered by these agents.	**D**

Point(s)
Clinical trial participation should be considered for patients with soft tissue sarcomas.

2.2.12 Radiotherapy

2.2.13 What is the evidence for radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage?

Recommendation	Grade
All patients with large, localised, high-grade extremity soft tissue tumours should be offered radiotherapy.	**B**
Omission of radiotherapy may be considered in select patients with small, superficial, extremity soft tissue tumours.	**D**

Point(s)
Radiotherapy does not compensate for inadequate surgery.

2.2.14 What is the evidence that pre-operative radiotherapy is superior to post-operative radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage and morbidity?

Recommendation	Grade
The timing of radiotherapy needs to be individualised dependent upon resection and reconstructive considerations.	**B**

Point(s)
Pre-operative radiotherapy may be the preferred approach in certain situations such as: A tumour of borderline resectability, and pre-operative radiotherapy may render it resectable. Radiosensitive histology (eg., myxoid liposarcoma), where tumour downstaging may be advantageous. Where adjacent critical structures (eg., brachial plexus) may limit the total dose of post-operative radiotherapy.

2.2.15 What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in truncal sarcomas?

Recommendation	Grade
In patients with non-metastatic truncal sarcomas, adding radiotherapy to surgery is appropriate to further improve local control. When offered, pre-operative radiotherapy is preferable to post-operative radiotherapy.	**C**

2.2.16 What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in retroperitoneal sarcomas?

Recommendation	Grade
In patients with non-metastatic retroperitoneal sarcomas, adding radiotherapy to surgery is appropriate to further improve local control. When offered, pre-operative radiotherapy is preferable to post-operative radiotherapy.	**C**

2.2.17 What are the indications for IMRT, brachytherapy, intraoperative radiotherapy (IORT), extra-corporeal radiotherapy and particle therapy in the management of BSTTs?

Recommendation	Grade
Brachytherapy (as an alternate or as a boost to external beam radiation) improves local control over surgery alone for high grade sarcomas for the limb and trunk.	**B**
IORT boost to external radiation could be considered in combination with surgery for management of retroperitoneal sarcomas.	**B**
It maybe reasonable to consider IMRT for patients with retroperitoneal and extremity /truncal sarcomas as adjuvant to surgery, if resource permits, for potential advantages in reduction of radiation dose to normal tissues.	**D**
Reconstruction using the patients own resected bone (previously bearing the sarcoma) fragment after a large extra-corporeal dose of radiation is a possible option reported to have satisfactory to good functional outcomes.	**D**

Recommendation	Grade
Particle beam therapy appears to offer good local control with acceptable toxicity.	**D**

2.2.18 Surgery

2.2.19 What are the factors influencing the extent of surgery in BSTTs?

Recommendation	Grade
It is important that wide surgical margin is achieved to prevent local recurrence and poor survival outcomes.	**B**
Musculoskeletal tumours are best managed in a specialist sarcoma unit by a multidisciplinary team.	**C**
Soft tissue sarcomas initially excised with residual disease and/or positive margins will require re-excision, preferably in a specialist sarcoma unit. These tumours should be re-excised with wide margins and usually require adjuvant radiotherapy.	**C**
Retroperitoneal sarcomas are best managed in a specialised tumour centre by a multidisciplinary unit.	**C**
Limb salvage surgery is an acceptable treatment in the management of osteosarcoma.	**C**
Pre-operative radiation therapy may allow preservation of vital structures without compromising local control.	**C**
Pre or post-operative radiation therapy should be considered in the management of soft tissue sarcoma. Decision should be made in the setting of a multidisciplinary team.	**A**
Isolated limb perfusion should be considered in patients with extensive soft tissue sarcoma where there is doubt whether limb salvage surgery can be achieved. Decision should be made in the setting of a multidisciplinary team.	**C**
Grade 1 Chondrosarcoma can be safely managed with intralesional excision with cementation. Distinction between this and other grades requires correlation of clinical and radiological features.	**C**

Point(s)
Any lump greater than 5 cm or deep to the deep fascia should be considered a sarcoma until proven otherwise.
Persistent and unremitting pain, not responsive to oral analgesics and nocturnal in occurrence should stimulate investigation for a bone tumour.
Complete imaging (anatomic and functional including XR, CT, MRI, nuclear scan) should be undertaken of a bone and soft tissue tumour prior to surgical manipulation.
Biopsy should be performed under image guidance to determine the track of the biopsy, and the target of the biopsy to confirm representativeness. Computed tomographic guidance is recommended. Biopsy should be performed after all imaging modalities have been completed to minimise the impact of biopsy induced image artifact.
Sarcomas are best managed at a specialist sarcoma unit.
Local recurrence is related to the adequacy of surgical margins. Wide surgical margins should be employed for bone and soft tissue sarcomas except when close margins are planned and adjuvant radiotherapy/chemotherapy is employed.
Tissues of different resistance to tumour invasion that surround a tumour may be used to calculate the quality of surgical margins. In this way, more careful planning of surgical margins may be undertaken when contemplating limb-sparing surgery.
Combination therapy is required to adequately manage bone and soft tissue sarcomas. Radiotherapy and wide margin surgery are used for soft tissue sarcomas. Chemotherapy and wide margin surgery are used for bone sarcomas.
Radiotherapy is recommended for low grade soft tissue sarcomas particularly if these tumours are large and excised with marginal margins.
Adequacy of surgical margins achieved should be assessed by a expert musculoskeletal pathologist. Refer to the Royal College of Pathologists of Australasia Soft Tumour Resection Structured Reporting Protocol 1st Edition 2011

2.2.20 What are the factors that impact on the choice of reconstructive options in BSTTs?

Recommendation	Grade
Provision of education and psychological support is an important component in holistic care of the sarcoma patient.	**C**

Recommendation	Grade
Referral to specialist hand and upper limb surgical team to be sought when surgical resection and reconstruction is required for sarcoma in the hand and forearm area.	**D**
Consider incorporation of thoracoplastic techniques with mesh and vascularised flap coverage in management of chest wall defects following sarcoma resection.	**C**
The decisions for reconstruction of skeletal elements are ideally made at a specialist sarcoma unit.	**D**
Sarcomas are better managed in a specialist sarcoma unit with planning of primary resection, reconstruction and timing of radiotherapy (where required) for optimal outcome.	**D**
Consider vascularised tissue coverage in management of soft tissue sarcomas, particularly when large resections or radiotherapy expected, and in children.	**C**
Recognise that pre-operative radiotherapy leads to a higher wound complication profile than (i) no radiotherapy, and (ii) post-operative radiotherapy.	**B**
Consider vascularised flap coverage (including free tissue transfer) in reconstruction of sarcoma defects following pre-operative radiotherapy.	**B**
Consider vascularised flap coverage (including free tissue transfer) in reconstruction of sarcoma defects when post-operative radiotherapy is anticipated.	**D**
When restoration of vascularity to a limb is required following sarcoma resection, prioritise arterial reconstruction and consider the need for venous reconstruction.	**D**
Consider vascularised tissue in reconstruction of bone and soft tissue in lower extremity sarcoma.	**D**
Consider vascularised tissue in reconstruction of bone and soft tissue in upper extremity sarcoma.	**D**

Point(s)
The nature of reconstruction of defects following sarcoma resection is often complex due to the required size of resection, likelihood of need for perioperative radiotherapy with associated surgical challenges, and variation in involved tissue types. Specialist Multidisciplinary Team management is advised for all cases for optimal outcome.
Optimisation of general patient factors, both physical (including diabetic control, nutrition, minimising smoking and avoiding preventable perioperative morbidity) and psychological, will provide benefits to patient outcome. Patient education regarding the disease process and treatment

Point(s)
options is also important in achieving the best holistic outcome.
Radiotherapy (in any form) reduces vascularity and impairs wound healing. Reconstructive options are affected by choice and timing of radiotherapy. A treatment plan for each case should be discussed at commencement of treatment to determine best timing and choice of surgical resection, surgical reconstruction and radiotherapy. This will allow best outcome with minimisation of surgical-related and radiotherapy-related morbidity.
When limb-preserving surgery is undertaken, care should be taken to reconstruct all resected tissues. This includes skeletal stability in bony reconstruction, reconstruction of neurovascular structures and functional muscle groups, and overlying soft tissue coverage.
In all resection defects requiring soft tissue coverage, vascularised tissue is the preferred reconstruction. This may be in the form of locoregional flap transfer, or free flap tissue transfer with reconstruction of the tissue vascularity using micro-surgical anastamoses of blood vessels. This enables best healing of underlying structures, reduces infection and other complication risks relating to skeletal implants, and provides greatest resilience to radiotherapy.
Restoration of function is the priority in reconstruction of the bony skeleton. Many options are available for reconstruction in metadiaphyseal areas, with preference for biological reconstruction where possible. Endoprosthetic reconstruction is commonly used in periarticular reconstruction.
Limb salvage procedures result in better functional outcomes, but do not necessarily result in greater quality of life.

2.2.21 What preoperative optimisation strategies improve outcomes in BSTTs?

Recommendation	Grade
Pre-operative embolisation may be considered in selected cases.	**D**
Pre-operative imatinib mesylate may be considered in selected patients with DFSP when surgery is difficult or potentially mutilating.	**D**

Point(s)
It is advisable to consider the suitability and applicability of pre-operative optimisation strategies, such as embolisation, prior to surgery for large or complex BSSTs.

2.2.22 What is the role of regional chemotherapy in BSTTs?

Recommendation	Grade
Isolated limb perfusion (ILP) may be considered as a palliative alternative to amputation in patients with extremity soft tissue sarcoma.	**D**

Point(s)
The toxicity of isolated limb perfusion (ILP) with melphalan is increased when combined with TNFα.
ILP may be considered to downstage extremity soft tissue sarcoma when primary amputation would otherwise be considered.

2.2.23 Follow-up

2.2.24 What are the measures to assess treatment response in BSSTs?

Recommendation	Grade
Functional imaging may assist standard methods of evaluating response to pre-operative chemotherapy or radiation therapy.	**D**

2.2.25 What is the ideal duration, frequency and modality of follow-up for BSTTs?

Recommendation	Grade
Regular clinical examination is part of routine surveillance for local recurrence.	**D**
High risk patients in whom pulmonary metastasectomy would be considered, are advised to undergo three to six month CT chest until five years.	**D**

Point(s)
Where the primary site is difficult to examine, for example the retroperitoneum or following complex

Point(s)
/flap reconstructions routine imaging may be appropriate.
Follow-up intervals recommended in current multinational guidelines are each three to four months in years one and two after diagnosis, six monthly in years three to four and annual thereafter. Late metastases may occur >10 years after diagnosis and there is no universally accepted stopping point for tumour surveillance. By contrast, the incidence of late effects of treatment increases with time. For patients enrolled in clinical trials, the above recommendations may vary in accordance with the follow-up protocols of these trials.
For patients considered suitable for pulmonary metastasectomy, low dose protocol non- contrast CT chest is the modality of choice for pulmonary surveillance.

2.3 Levels of evidence and grades for recommendations

The following table provides a list of the evidence-based recommendations detailed in the content of each topic question. The table below provides details on the highest level of evidence identified to support each recommendation (I-IV). The Summary of Recommendations table includes the grade for each recommendation (A-D). The key references that underpin the recommendation are provided in the last column. Individual levels of evidence can be found in the Evidence Summaries for each recommendation in each question.

Each recommendation was assigned a grade by the expert working group taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence supporting each recommendation. When no Level I or II evidence was available and in some areas, in particular where there was insufficient evidence in the literature to make a specific evidence-based recommendation, but also strong and unanimous expert opinion amongst the working group members about both the advisability of making a clinically relevant statement and its content, recommended best practice points were generated. Thus, the practice points relate to the evidence in each question, but are more expert opinion-based than evidence-based. These can be identified throughout the guidelines with the following: Practice point (PP).

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Grade of recommendation	Description
PP (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Adapted from: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Level of evidence was assigned according to the following criteria from the NHMRC Evidence Hierarchy[1]:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised	A retrospective cohort study	A comparative study with concurrent controls: ■ Non-randomised, experimental trial

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
	■ Interrupted time series with a control group		controlled trial		■ Cohort study ■ Case-control study
III-3	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study ■ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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2.4 References

1. ↑ [1.0] [1.1] National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers.* Canberra: National Health and Medical Research Council; 2009 Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

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2.1 Impact of referral delay

Contents

2.1.1 What is the impact of delay in referral to a specialist centre in BSTTs?

2.1.1.1 Introduction

Delay in instituting definitive management of sarcoma can arise through a variety of mechanisms, including patient delay in presentation (time between onset of symptoms and first seeking medical advice), and medical delay (in referring the patient to a specialist centre). Medical referral delay may arise through failure to recognise the problem e.g. thinking that a soft tissue mass is a harmless lipoma, delays in obtaining complicated imaging or other assessments e.g. waiting for a CT scan or biopsy, or referral to a non-specialist unit or surgeon who lacks specific expertise in sarcoma, who may then also delay referring the patient on to a specialist centre, or fail to do so at all. Before reaching a specialist unit, the patient may have been falsely reassured and had no intervention at all, or have had inappropriate or inadequate investigations and/or surgery prior to definitive management, and in some cases will only finally reach a specialist unit (if at all) after local and /or distant recurrence.[1] Whatever the cause of delay, there is evidence that delayed referral to a specialist centre (or failure to refer at all and managing the patient in a non-specialist unit) impacts on patient outcomes.

2.1.1.2 Definition of delay

There is no clear consensus as to what constitutes a “delay” in referral or, by extrapolation, what time interval is acceptable. Definitions of delay range from greater than three weeks[2] to “more than a month”[3] to three months or more,[4] but it is clear that many patients have symptoms for some months or even years before reaching a sarcoma unit. Patient-related delay in presentation can be as long as twenty-six months,[3] and medical delay in referral even longer: ten years in one extreme example,[3] but more often from a few months [5] to around a year.[3][4]

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2.1.1.3 Impact of referral delay on subsequent management

The most obvious result of a delay in definitive management is tumour progression (either growth of the primary or, potentially, the development of distant metastases). But inexpert attempts at management e.g. delaying specialist referral while waiting for imaging or biopsies, may also impact on subsequent management. Many studies[3][4][5] [6] have highlighted the frustration felt by specialist centres when patients are referred after undergoing inappropriate or inadequate “work-up”, which then needs to be repeated before definitive treatment can be instituted, resulting in further delay. In one study of 100 consecutive patients referred to a specialist unit,[3] 63 had undergone “complex” imaging prior to referral, and in 56 of these, further imaging was performed to obtain information that was considered necessary to plan treatment.

Even more concerning are the cases where inappropriate or inadequate biopsy, or incomplete excision, have been undertaken prior to referral. Apart from the delay incurred in repeating a previously non-diagnostic biopsy, in many cases a poorly planned biopsy may impact on subsequent management such as requiring more radical surgery, compromising flaps or necessitating adjunctive chemo- or radiotherapy which might otherwise have been avoided. For example, in the study by Ashwood et al.[3] 34 of the 100 patients had undergone biopsy or surgery prior to referral, which complicated further treatment in 16 of these. Two studies by Mankin et al.[7][8] more than a decade apart showed strikingly similar results: in the first study[7] 34% of patients undergoing biopsy prior to specialist referral had “non-representative or technically poor” biopsies. The subsequent management plan was altered in 18.2% because of biopsy-related problems in the first study and 19.3% in the second.[8]

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2.1.1.4 Impact of referral delay on patient outcomes

Some patients are not referred to a specialist unit at all but are managed in a non-specialist centre, and (at least in the UK) these patients have been found to have lower survival rates.[9] But even a delay in referral can impact on the patient's clinical course: Clark & Thomas [4] found a referral delay of greater than three months to be "likely to have had a detrimental effect" on treatment options and outcomes in one fifth of patients and other studies have shown a correlation between the duration of symptoms prior to treatment and disease relapse, distant metastases and survival[10][11] and with chemoresponse.[2] Conversely, Han et al.[12] found no significant difference in disease-free survival or local recurrence according to time to definitive surgery, but positive surgical margins and greater tumour size were predictive of local control.

In the two studies by Mankin et al. referred to above,[7] [8] prognosis or outcome was considered to have been affected by pre-referral biopsy in 8.5% of patients in the first study[7] and 10.1% in the second.[8] These effects ranged from more radical surgery resulting in loss of function and long-term disability to increased rates of local recurrence and mortality. And patients who were referred after undergoing initial surgery in nonspecialist units underwent a greater number of operations and more often experienced local recurrence, than those who were referred directly to a specialist unit.[13]

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2.1.2 Evidence summary and recommendations

Evidence summary	Level	References
Delays in referral to specialist sarcoma units are common and sometimes lengthy, often have adverse consequences for subsequent patient management, and may well impact on patient outcomes.	IV	[1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13]

Evidence-based recommendation	Grade
Immediate referral to a specialist sarcoma unit to be sought when a tumour of bone or soft tissue (other than simple lipoma) is suspected.	**D**

Practice point

In practice, any mass lesion greater than 5cm in size, and lesions deep to or attached to deep fascia, should be considered a sarcoma until proven otherwise.

Practice point

Refer to a specialist sarcoma unit.

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2.1.3 Issues requiring more clinical research study

A gap in the evidence has been identified:

- What are the barriers to diagnosis and treatment of sarcoma and their impact on patient outcomes?

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2.1.5 Appendices

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2.1.6 Further resources

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2.2 Efficacy and accuracy of various biopsy modalities

Contents

2.2.1 What are the relative rates of efficacy and accuracy of various biopsy modalities in BSTTs?

2.2.1.1 Fine needle versus core versus open biopsy

2.2.1.1.1 Introduction

Patients with suspected bone and soft tissue tumours (BSTTs) require accurate diagnostic biopsy prior to definitive treatment. Various biopsy techniques which are used include fine needle aspiration (FNA) cytology, needle core biopsy (NCB) and open (incisional) biopsy. Open biopsy was long heralded as the 'gold standard' in the diagnosis of BSTTs, but with the advent of less invasive procedures of FNA and NCB, use of this more invasive procedure has diminished.[1] FNA and NCB are less expensive, less invasive, have a lower complication rate than open biopsy and generally do not lead to modification of the definitive surgical procedure.[2] FNA and NCB allow for multiple passes to be performed in various directions increasing accuracy of subtyping, although theoretically this may impart a greater risk of recurrence or tumour spread.[3]

The diagnostic benefits of various biopsy techniques have been reviewed in predominately retrospective studies including studies assessing open biopsy alone,[4] of FNA alone[3][5][6][7][8][9][10][11][12][13][14][15][16][17], of NCB alone,[2][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36] or biopsies performed in various combinations[1][37][38][39][40][41][42][43][44] Rougraff et al[45] performed an extensive evidence based literature search on soft tissue biopsy modalities.

The ubiquitous view in the literature is that all techniques should ideally be carried out in a multidisciplinary team setting.[19][21][28][36]

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2.2.1.2 Rates of efficacy/accuracy of the various biopsy modalities

Although open biopsy is regarded as the "diagnostic standard to which all alternative biopsy techniques must be compared", it may still be non-representative and technically poor.[23] The reported diagnostic accuracy lies between 88% and 100%.[4][12][42][43][44] Higher accuracy may be achieved with intraoperative frozen section assessment.[12][44] Open biopsy allows the advantage of more tissue to be harvested to enable a broad range of ancillary studies. However, it requires general anaesthetic, care is needed to avoid an inappropriately placed incision which widens the required definitive resection size and it has a reported complication rate of 12-17% including haematoma, infection, wound dehiscence and tumour fungation.[2] However, the risk of complication may not be as high if performed by an experienced surgeon.[4]

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2.2.1.2.1 Fine needle aspiration

FNA has the advantage of low cost, quick turnaround time and low incidence of complication.[6][10] It has been considered to be a first-line investigation,[5] as a simple method of patient triage[6] or as a screening test.[14] Studies tend to report accuracy with regard to general parameters such as benign versus malignant, as FNA

lacks the ability to assess tissue architecture.[8] As a result, sarcoma grading methods including the FNCLCC and NCI systems, which require tissue morphology as a whole, may not be applicable[10] and limited cytological grading based on cellular pleomorphism is often employed. Reported accuracy rates for detecting sarcoma are as low as 60.5%[6] to as high as 98% for categorisation as benign versus malignant, rather than giving a definitive diagnosis.[39] Correct classification/subtyping of soft tumours may only be achievable in 50-60% of cases because of the inherent heterogeneity of soft tissue tumour types.[7][17] Significantly, absence of tissue architecture in an FNA sample makes assessment difficult and subtyping less accurate than tissue biopsy.[16]

Myxoid lesions may have the highest propensity to fall into a “suspicious for malignancy” category, whilst spindle cell lesions appear to be the most difficult in which to render a specific diagnosis.[14] In bone lesions, the limitation of FNA has been the inability to obtain adequate diagnostic material from intraosseous, sclerotic and low-grade tumours.[9] As the diagnosis of a primary bone tumour is often made radiologically, FNA may be a confirmatory rather than diagnostic test in that setting.[10] It may be an efficient method in the diagnosis of primary osteosarcoma in conjunction with radiological and clinical data.[8] In one study, chondrosarcoma caused greatest diagnostic difficulty and Ewing sarcoma the least.[13] Fibroosseous lesions are also associated with sampling error.[12] Specific sites such as the hand, where a limited number of common soft tissue tumours occur, may result in higher diagnostic accuracy.[3]

Ancillary studies can increase the accuracy of FNA, which may include cell-block for morphology, immunohistochemical and molecular studies and flow-cytometric immunophenotyping.[6][9][11][44][17] Successful FNA is also highly dependent upon the experience of the cytopathologist and close collaboration with the orthopaedic surgeon.[16] CT-guided FNA accuracy rates may be lower than NCB because it is more operator and cytopathologist dependent and less material may be obtained for ancillary studies.[1]

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2.2.1.2.2 Needle core biopsy

NCB, which may also be performed blind or with image guidance, is touted as the ‘new gold standard’ in the diagnosis of musculoskeletal tumours including of the spine.[30][31] It is reported to be equally effective in BSTTs, but this may depend on site. One study reported only 33% accuracy in abdominal wall tumours.[19] Conversely, high accuracy was reported in a study on the diagnosis of chest wall sarcomas.[46] Overall accuracy is lower but comparable to that of open biopsy,[44][45] and ranges from 71%[1] to near 100%.[20] It may be less accurate in soft tissue compared to bone as bone tumours often show specific imaging features, lacking in soft tissue tumours.[26][29] In bone, diagnostic yield may be higher for lytic than sclerotic lesions.[35] Accurate tumour subtyping and grading is achieved from 45.6%[44] to or exceeding 90%.[25][40][26][31][2][34][41] Grading is also more accurate in high-grade tumours.[38][29]

NCB may show higher accuracy in grading than open biopsies if they are performed in a number of directions as they may sample more representative areas of a tumour, in contrast to sampling a single area in an incision biopsy.[24] Adequate NCB sampling is also important to avoid misclassification due to tumour heterogeneity.[25] Rimondi[30] heralded NCB as the new gold standard in biopsy of the spine, although false negative results were recorded in cervical lesions. Jelenek[39] recorded a high accuracy for both sclerotic and non-sclerotic lesions in primary bone tumours, but noted difficulty with cystic lesions. Diagnostic accuracy of NCB of sclerotic lesions of the spine was only 76% compared to 93% in lytic and mixed sclerotic/lytic lesions in a study by Lis.[40]

Factors which have been shown to optimise the diagnostic yield of NCB, include the use of contrast-enhanced ultrasound[21] and PET-scan guidance[22] to detect the areas of a tumour which are most representative (i.e. with the worst histological features). In particular, myxoid lesions, which may cause diagnostic difficulty by NCB [42] have showed improved diagnostic accuracy with contrast-enhanced ultrasound guidance.[21] Vacuum assisted NCB showed overall 96% diagnostic accuracy compared to 99% by open biopsy in a study by Mohr.[43] NCB adequacy by frozen section assessment in one study increased accuracy rate to near 100%.[20] The diagnostic yield of CT or ultrasound guided NCB of BSTTs was shown to be greater with higher tissue yield by using longer needle cores and a minimum of 3 and 4 cores for the diagnosis of BSTTs respectively.[35] In ultrasound guided NCB of soft tissue tumours, technical factors such as the number of cores, NCB gauge, experience of operator or site of biopsy had no influence on diagnostic yield when performed in a specialist department.[27]

Some studies have compared the use of both FNA and NCB taken in the same procedure, or assessed their accuracy together.[37][38][1][39][40][41] Hau[1] had a diagnostic accuracy by FNA and NCB of 63% and 74% respectively. They found that pelvic lesions had the most diagnostic accuracy (81%), where as there was low accuracy of 61% for any lesion located in the spine. For both FNA and NCB, more tissue is required for diagnosis in low grade and benign lesions than for high-grade malignant tumours.[41] Kasraelian[44] performed FNA then NCB followed by open biopsy in a single procedure, the latter assessed by frozen section in a series of 57 patients. NCB was more accurate than FNA in determining malignancy, exact diagnosis and grade, and open biopsy was more accurate than both.[47]

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2.2.2 Evidence summary and recommendations

Evidence summary	Level	References
FNA has a lower diagnostic accuracy than NCB, which itself has a lower diagnostic accuracy than open biopsy, but a rate that is never-the-less acceptable in light of it being a simple, less costly method, with a low complication rate. All techniques have higher accuracy if assessed at the time of collection by a pathologist, and if ancillary techniques are utilised where relevant.	IV	[44], [45]

Evidence-based recommendation	Grade
Biopsy technique of choice is needle core biopsy (NCB) performed in a specialist sarcoma unit setting with appropriate multidisciplinary input.	**D**

Practice point
In essence, generous numbers of needle cores of adequate length, performed with the aid of imaging, in various directions within the tumour, allows for tumour heterogeneity. In most cases this results in accurate diagnosis, grading and harvesting of adequate tissue for appropriate ancillary diagnostic techniques and, in appropriate circumstances, tissue banking. Refer to the Royal College of Pathologists of Australasia Soft Tissue Tumour Resection Structured Reporting Protocol 1st Edition (2011)

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2.3 Imaging modalities

Contents

2.3.1 What are the most appropriate imaging modalities for diagnosis and staging of BSTTs?

2.3.1.1 Introduction

Many bone and soft tissue tumours (BSTTs) are found unexpectedly when a General Practitioner (GP) orders an imaging test investigating a lump or pain. These initial tests may be an x-ray, ultrasound or computed tomography (CT) scan.

If a sarcoma is expected, it is recommended not to proceed to biopsy until there has been further imaging and review by a surgeon.

Aims of imaging at diagnosis and staging are:

- Assess bone marrow involvement and extra-osseous soft tissue mass
- Identify involvement of adjacent neurovascular bundles
- Define location of soft tissue tumour within muscular compartments
- Detect nodal and metastatic spread
- Plan site and route for biopsy
- Plan resection

2.3.1.2 Assessing the primary lesion

For bone and soft tissue masses in the extremities, magnetic resonance imaging (MRI) with intravenous contrast provides excellent visualisation of the tumour, soft tissue extension and relationship to surrounding structures. Post contrast, fat saturated MRI sequences help differentiate tumour from adjacent soft tissue oedema.[1][2][3] [4] [5][6][7] If MRI is contra-indicated, contrast enhanced CT provides useful information.[8] CT is better at detecting subtle cortical erosion and periosteal reaction.[9][10] PET-CT can be useful for initial grading and guidance of biopsy.[11][12]

For soft tissue sarcomas (STS) in the abdominal cavity, a post contrast CT provides excellent multiplanar information regarding the relationship of the tumour to adjacent structures. There is limited evidence comparing CT and MRI in the abdominal cavity for STS, but in practice, contrast enhanced CT is a reliable investigation which can usually provide all of the required information. Only in selected cases is MRI required to add further relevant information for treatment planning.

MRI with magnetic resonance venography (MRV) is useful in primary intraluminal leiomyosarcoma of the Inferior vena cava (IVC).[13]

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2.3.1.3 Staging investigations

Aim to identify nodal and metastatic disease at the time of diagnosis.

A CT chest is commonly recommended at initial staging of all sarcomas due to the risk of metastases to the lungs. While this is included in many sarcoma guidelines, there is little evidence showing a significant detection rate in the setting of a normal chest x-ray at diagnosis. It is argued that the yield is low in T1 primary extremity STS.[14]

For lower limb soft tissue tumours, a CT abdomen and pelvis can be used to assess for lymph nodes.[15] In children ultrasound can be used to assess for regional lymph nodes.

Combined positron emission tomography and computed tomography (PET-CT) using 18F-fluorodeoxyglucose (FDG) can improve overall accuracy of staging soft tissue sarcomas. The degree of uptake varies with tumour grade and cell type. Whole body PET-CT can be useful for staging of STS, especially prior to radical surgery to identify unexpected metastases. However, suspicious lesions may need to be confirmed with biopsy due to a risk of false positives from inflammation. PET-CT can also guide biopsy to the most aggressive site within the primary mass.[11][12][16][17][18][19]

Whole body bone scan (WBBS) is a traditional staging investigation for bone metastases in sarcoma, but has an inferior sensitivity to PET-CT.[20][21][22]

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2.3.1.4 Biopsy

Ideally the biopsy is performed after the staging scans. This should be done after consultation with a surgeon and by a radiologist familiar with the issues of sarcoma biopsy. This takes into consideration the area of the tumour most likely to yield results and the likely surgical approach.

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2.3.2 Evidence summary and recommendations

Evidence summary	Level	References
For suspected bone and soft tissue tumours (BSTTs) in the extremities, MRI with intravenous contrast provides excellent visualisation of the mass, soft tissue extension and relationship to surrounding structures.	III-2, IV	[23], [2], [3], [4], [5], [6], [7]

Evidence-based recommendation	Grade
Magnetic resonance imaging is the imaging modality of choice for extremity tumours.	**B**

Practice point
CT is usually adequate for abdomino-pelvic masses.

Practice point

Further imaging and biopsy only performed after review by a surgeon or other member of a sarcoma team.

Practice point

CT chest be performed at diagnosis to assess for metastatic disease.

Practice point

PET-CT may be used prior to radical surgery of soft tissue sarcomas.

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2.4 Sentinel node biopsy

Contents

2.4.1 Lymph node involvement in sarcoma

Lymph node involvement in sarcoma is generally uncommon (1%)[1], though it does occur with increased frequency in certain pathological subtypes. This is particularly true for rhabdomyosarcoma, a tumour that is more common in the paediatric and younger adult population, and several other tumour types, more common in adult patients, as shown in the table below.

Pathological type	Lymph node involvement	References
Rhabdomyosarcoma	6-32%	[2][3][1][4][5]
Epithelioid sarcoma	13-32%	[2][3][1][4]
Clear cell sarcoma	11-28%	[2][1][4]
Angiosarcoma	8-24%	[2][3][1][4]
Leiomyosarcoma	4-8%	[5][1][4]
Synovial sarcoma	1-6%	[2][1][4]
Osteosarcoma	3%	[6]

Other tumour characteristics that increase the likelihood of lymph node involvement include grade of tumour (high grade more likely) and increased tumour size (>5cm more likely).[1][4] Both of these have much smaller effect than the pathological subtype.[1]

Involvement of the lymph nodes significantly reduces prognosis in sarcoma patients. Johannesmeyer et al. report a five-fold increase in mortality in soft tissue sarcoma when lymph nodes are involved[1], and this is mirrored in osteosarcoma[6]. Protocols recommended by the Childrens Oncology Group for the management of rhabdomyosarcoma, and epithelioid sarcoma and clear cell sarcoma[3] in children recommend staging of the regional lymph nodes to direct optimal management. Studies in breast malignancy show that sentinel node biopsy is more sensitive in detecting metastatic disease than unguided lymph node sampling.[7] In these groups, sentinel node biopsy should be considered as the method for lymph node assessment.

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2.4.2 Lymph node assessment in sarcoma

Pathologically enlarged lymph nodes can be identified clinically and on standard radiology (CT), and subsequently can be investigated by biopsy and pathological examination. Standard biopsy is through open surgical biopsy or core biopsy of the enlarged lymph node. Fine needle aspirate of an enlarged lymph node is rarely used in sarcoma management. Fine needle aspiration cytology may be acceptable when the pathology team also has access to the primary specimen for comparison.[8]

When lymph nodes are not pathologically enlarged, clinical and radiological assessment are insufficient to completely assess nodal status in sarcoma. Neville reported that 17% of regional nodal basins that were assessed as uninvolved clinically actually harboured micrometastases.[9] CT and PET are important staging tools for systemic disease, but are also not sensitive enough to detect lymph node micrometastases.[10]

Sentinel lymph node biopsy (SLNB) is a tool used commonly in breast carcinoma and melanoma to target the most likely node within a lymph node basin to be affected by micrometastatic disease. A combination of radio-isotope labelled dye and coloured dye techniques are used to identify the sentinel node and this is assessed histo pathologically. Multiple studies confirm the safety and efficacy of this tool in identifying micrometastatic disease in lymph nodes for sarcoma patients with increased risk of lymph node metastases. [10][11][12][13][14][15][16][17][18][19] Sentinel node biopsy can also identify the relevant nodal basin in areas where drainage patterns can be variable, such as the torso.

The use of SLNB in sarcoma was felt to impact on treatment decision making[14][20], and provide important prognostic information[20].

The table below shows the rate of identification of lymph node involvement:

2.4.2.1 Paediatric

Tumour type	Age group	Positive/total SLNB (%)	References
RMS Non-RMS	Paediatric	2/5 (40%) 0/3 (0%)	[10]
RMS Non-RMS	Paediatric	2/10 (20%) 1/18 (6%)	[12]
RMS Non-RMS	Paediatric	1/3 (33%) 0/7 (0%)	[13]
RMS Non-RMS	Paediatric	1/9 (11%) 0/17 (0%)	[14]
RMS Non-RMS	Paediatric	1/3 (33%) 0/2 (0%)	[16]
RMS Non-RMS	Paediatric	1/6 (17%) 0/17 (0%)	[17]
Summary			

Tumour type	Age group	Positive/total SLNB (%)	References
RMS Non-RMS	Paediatric	8/36 (22%) 1/64 (2%)	[10][12][13][14][16][17]

RMS = Rhabdomyosarcoma

2.4.2.2 Adult and mixed ages

Tumour type	Age group	Positive/total SLNB (%)	References
Synovial sarcoma Clear cell sarcoma Epithelioid sarcoma Rhabdomyosarcoma	Mixed	2/42 (5%) 6/12 (50%) 0/4 (0%) 0/4 (0%)	[11]
Synovial sarcoma Clear cell sarcoma Epithelioid sarcoma	Mixed	2/16 (13%) 0/3 (0%) 1/10 (10%)	[15]
Synovial sarcoma	Adult	1/11 (9%)	[18]
Clear cell sarcoma	Adult	2/5 (40%)	[19]
Summary			
Synovial sarcoma Clear cell sarcoma Epithelioid sarcoma Rhabdomyosarcoma	Mixed	5/69 (7%) 8/20 (40%) 1/14 (7%) 0/4 (0%)	[11][15][18][19]

SLNB is accepted as a reasonable tool to assist prognosis in melanoma when the rate of positive results is 10% or greater. Applying this general recommendation, the use of SLNB in sarcoma should be considered in rhabdomyosarcoma. This could also be considered in other subtypes with higher rates of lymph node metastasis.

Technical aspects of the SLNB were generally very similar, though there was slight variation in dye injection site. Some studies placed the dye in the soft tissues adjacent the tumour (peritumour)[10][11][16][18], and some studies placed the dye intradermally over the tumour[12][13][14][15][17][19]. The latter approach is accepted in breast carcinoma where the involved organ is subcutaneous, but many sarcomas arise in deeper tissues (e.g. muscle) where different lymph drainage patterns may occur. Both approaches identified positive sentinel nodes and had episodes of nodal involvement after negative sentinel node biopsy. One group adopted an approach to only use the radio-isotope labelled dye (and no coloured dye) with good results, and removal of the recognised risk of anaphylaxis to the commonly used coloured dyes, but had insufficient patients to show a definite benefit.[14]

Several papers described lymph node involvement developing in regional nodes after previously negative SLNB in sarcoma[15][18] A study reviewing sentinel lymph node biopsies in sarcoma, suggested that 7 of 100 cases developed lymph node metastases after negative SLNB.[20] On further review of the original studies[14], and correction of a calculation error by Wright[20], this is actually 5 of 100 or 5%.

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2.4.3 Evidence summary and recommendations

Evidence summary	Level	References
Sentinel lymph node metastases are identified in 22% of paediatric patients with rhabdomyosarcoma. Sentinel lymph node biopsy in rhabdomyosarcoma can assist management and guide prognosis.	IV	[10], [12], [13], [14], [15], [16], [17]
Sentinel lymph node metastases are identified in 40% of clear cell sarcoma patients, and 7% of synovial sarcoma and epithelioid sarcoma patients.	IV	[11], [15], [18], [19]
Sentinel lymph node biopsy is a more accurate technique to stage regional lymph nodes when indicated.	IV	[7]

Evidence-based recommendation	Grade
Sentinel lymph node biopsy should be considered as a lymph node staging tool in the management of sarcoma patients with high likelihood of lymph node involvement, particularly rhabdomyosarcoma.	**D**

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2.4.4 Future questions

1. Does sentinel lymph node biopsy improve staging in sarcoma, particularly in relevant tumour types (e.g. rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, angiosarcoma)?
2. In sentinel lymph node biopsy for sarcoma, what is the preferred technique (intradermal/peritumour placement, use of just radio-labelled or both radio-labelled and coloured dyes)?
3. In sentinel lymph node biopsy for sarcoma, what is the preferred technique of histological assessment of biopsy material?

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2.4.5 References

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2.5 Prognostic factors

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2.5.1 What is the role of prognostic factors in management of BSTTs?

2.5.1.1 Introduction

Current staging systems may not consider sufficient variables to predict outcome, and as sarcoma is a rare tumour it is unlikely that many clinicians or even centres will accumulate enough experience to reliably predict the prognosis of individual patients. Fortunately, some institutions have been able to analyse large series of patients and identify factors associated with prognosis.[1][2][3][4][5][6][7][8][9] At present most reports are generated from the analysis of patients who have undergone surgical resection. Some studies report the factors influencing prognosis after local or distant recurrence.[10][11][5][12][13] Prognostic algorithms and nomograms (graphical representations of probabilities based on multiple variables) are therefore important for multidisciplinary teams managing patients with sarcoma. Not only do these tools allow prediction of prognosis, they inform the need for adjuvant therapies and allow stratification of risk for consideration of entry into clinical trials.[14][6]

2.5.1.2 Sarcoma Subtypes

Due to the many tumour subtypes and locations it is unlikely that any institution or group will be able to provide a comprehensive assessment of the relevant prognostic factors for all sarcoma subtypes. As a result published reports consider either several tumour types and/or sites grouped together or a single tumour type or site.[15][8][9] Unfortunately, reports often contain small numbers of patients, treated with heterogeneous protocols. The studies vary widely in methodology and quality. Single-institution studies may also lack generalisability. In particular, institutions may treat patients within certain age ranges or of certain ethnicity. Published series focus on groups of patients with osteosarcoma, Ewing's family tumours and soft tissue sarcoma (STS).

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2.5.1.2.1 Osteosarcoma

Osteosarcoma is the most common bone sarcoma with an incidence of approximately three per million. It has been one of the success stories of cancer therapy as over the past forty years survival has improved from 15% to over 70%. This is likely to be the result of advances in systemic therapy.[16][17][18][19] Surgical treatments have also evolved so that limb-sparing surgery is now possible in around 90%. The most recent review of prognostic factors was able to identify only seven papers with sufficient data or statistical analysis to allow re-examination. The authors concluded that response to chemotherapy is an independent prognostic factor, a poor response increasing the risk for dying of the disease possibly approximately 2.4 times. Several other factors may have some prognostic importance but their value is difficult to calculate. These include tumour size, excision margin, ablative surgery, age, male sex, serum alkaline phosphatase level, local recurrence, p-glycoprotein expression, and Erb2 expression.[20]

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2.5.1.2.2 Ewing's Sarcoma Family tumours

Ewing's sarcoma family tumours are a group of histologically similar small round blue cell tumours that share common chromosomal translocations, most commonly t(11;22) resulting in a fusion gene involving EWS and FLI1. The group contains Ewing's sarcoma of bone, Askin's tumour (a characteristic Primitive Neuroectodermal Tumour (PNET) arising in the thorax) and soft tissue Ewing's or PNET. Rhabdomyosarcoma is typically a childhood cancer which shares with Ewing's family tumours the appearance of small round blue cells but has immunohistochemical features of skeletal muscle. Approximately 80% of this family of tumours occur in patients under twenty years of age.[21] All of these tumours are rare and Ewing's tumours of bone make up approximately 3% of all paediatric malignancies.[22][23][24][25]

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2.5.1.2.3 Soft tissue sarcoma

As there are around fifty subtypes of STS it is unlikely that prognostic factors will be able to be determined for each type. Historically, most series group soft-tissue sarcoma subtypes and report outcomes based on tumour site. However, as datasets have increased there are more tumour type-specific reports of outcomes.[26][15][27] [13][6][8]

Extremity tumours

The limbs (and limb girdles) are the main site of sarcomas. The preservation of limb function is a major focus of treating teams. It appears different factors affect local and distant recurrence.

Trunk tumours

Approximately 20% of sarcomas are located in the trunk. Studies may include visceral tumours in this group but generally retroperitoneal tumours are excluded. Low-grade lesions such as dermatofibrosarcoma protuberans (DFSP) and desmoids are usually excluded from reports of prognosis.

Retroperitoneum

The retroperitoneum is the site of approximately 15-20% of sarcomas. Operability has long been considered the major determinant of outcome.[28][29][30] To date adjuvant therapies have shown little benefit.

Head and Neck

The head and neck are the sites of between 5% and 15% of sarcomas. Due to the presence of vital structures radical resections are difficult or impossible.

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2.5.2 Evidence summary and recommendations

Evidence summary	Level	References
Predictive models and nomograms have been developed by the analysis of outcomes of large series of patients. These may be used to counsel patients and to identify their need for adjuvant therapies.	IV	[2], [14], [31], [32], [33], [34], [35], [36], [37], [6], [38], [7], [8]
The improvement in outcome of patients with osteosarcoma is largely due to the inclusion of systemic chemotherapy into the treatment regimen. Tumour response to chemotherapy appears to be the most potent predictor of survival. Tumours situated in the distal limb are associated with improved survival rates.	IV	[32], [20], [39], [16], [18], [17], [40], [19]

Evidence summary	Level	References
The improvement in outcome of patients with Ewing's family/PNET is largely due to the inclusion of systemic chemotherapy into the treatment regimen. Tumour response to chemotherapy appears to be a potent predictor of survival. Tumour volume is also a significant predictor of outcome so earlier diagnosis is likely to be helpful. The prognostic factors for patients with skeletal and extra-osseous Ewing's tumours are similar.	IV	[41], [42], [43], [44], [22], [45], [21], [24], [23], [25]
Until recently it was uncommon for a single sub-type of soft-tissue sarcoma to have been studied sufficiently to provide reliable prognostic information. Instead most authors report prognostic variables for patients with tumours grouped by site. There are now several case series reporting prognostic information for specific tumour sub-types.	IV	[33], [46], [14], [31], [2], [47], [11], [48], [10], [49], [50], [51], [52], [8]
For extremity tumours, tumour grade, excision margins and patient age influence rates of local recurrence. Tumour grade, size and depth influence distant recurrence and death. The use of radiotherapy may improve local control. Outcomes may be better when patients are treated in specialised centres.	IV	[31], [53], [33], [54], [34], [48], [35], [32], [55], [56], [36], [57], [51], [58], [52], [59]
For truncal tumours, tumour grade, excision margins, tumour size and the use of radiotherapy influence local and distant recurrence.	IV	[31], [30], [60], [35], [61], [38], [46]
Retroperitoneal tumour site confers a worse prognosis for most tumour types. Tumour grade and excision margins influence survival. High-grade histology may be associated with a five-fold increase in death. As yet there is no evidence that pre-operative therapies improve disease-specific survival. There is some evidence that only tumour grade remains a significant prognostic factor one year after diagnosis.	IV	[15], [6], [28], [31], [30], [62], [2], [14], [1], [47], [63], [64], [65], [66], [67], [68], [69], [70], [29], [9]
For tumours of the head and neck, excision margins influence local recurrence. Tumour grade, patient age and the development of local recurrence influence overall survival.	IV	[71], [72], [73], [74], [75], [76], [77], [78], [73], [79],

Evidence summary	Level	References
		[80], [81], [82], [83]
Recent publications have examined the role biochemical and haematological markers may play in predicting prognosis. Modifications to current staging systems may be required to accommodate contemporary staging methods.	IV	[84], [19], [85], [86], [87], [7]

Evidence-based recommendation	Grade
Statistical models assessing the influence of prognostic factors can be used to counsel patients and to stratify their need for adjuvant therapies or entry into clinical trials.	**D**

Practice point
Accurate data collection will facilitate further study in this area. Tissue banking will allow further assessment of tumours as new diagnostic and therapeutic modalities emerge.

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2.5.3 Issues requiring more clinical research study

- Can prognosis be estimated from percutaneous biopsies?
- Is it possible to identify optimal treatment sequencing from percutaneous biopsies?

2.5.4 References

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2.6 Second opinion on BSTT pathology

Contents

2.6.1 What is the outcome of a second opinion in BSTT pathology?

2.6.1.1 Introduction

As bone and soft tissue tumours (BSTTs) are collectively uncommon and individually comprise many rare entities, pathologists outside specialist sarcoma units will have limited opportunity to develop expertise in their diagnosis. This has been made even more challenging in the past decade, with an increasing trend to preoperative diagnosis by core needle biopsy (which provides limited material for ancillary studies and makes appreciation of tumour heterogeneity and diagnostic architectural features more difficult). Therefore, whenever a sarcoma is biopsied or even possibly resected outside a specialist multidisciplinary team (MDT) setting, timely review of the diagnosis (including histologic subtype and grade) is warranted.

2.6.1.2 Expert pathologist review

Clearly this sort of question does not lend itself to investigation through a randomised trial; but there is ample and consistent “low level” evidence that expert review results in a change to diagnosis in a significant proportion of cases (ranging from a minor disagreement over tumour grade, which may nonetheless influence treatment decisions, to a false positive - or false negative - diagnosis of malignancy. Expert review of cases may occur in a variety of settings, for example:

1. initial diagnosis of sarcoma results in referral to a specialist centre, and the sarcoma MDT’s pathologist undertakes routine review of original material from another centre
2. diagnostic material is sent for central review as part of a clinical trial
3. studies conducted through institutions or tumour registries specifically review “outside” diagnoses to investigate this question
4. the “non-expert” pathologist is aware of their limitations in this area and sends a difficult case for an “expert” second opinion
5. initial material (biopsy and/or resection) is reviewed when the patient’s clinical course seems out of keeping with the initial diagnosis

Clearly one would expect the level of discrepancy between the referring and receiving pathologists’ diagnoses to be greater in the last case, but even in examples 1-3 the level of disagreement can be disturbingly high. In some cases, discordant results may have little or no impact on the patient (such as particular sub-types of high grade sarcoma for which management will be the same), but in other cases the impact of a discordant diagnosis may be significant. For this reason, many studies in this area divide the rates of discordance along the lines of “minor” and “major” disagreement, as well as an overall “concordance rate”. Disturbingly, reported rates of overall discordance approach or even exceed 50% in some studies,[1][2][3] with even “major” disagreement occurring in over 25% of cases,[4][5] but more often between 10 and 20%.[6][3][7] And in some cases there is even disagreement over whether a tumour is truly a sarcoma, or another malignancy (typically melanoma, carcinoma or germ cell tumour), or a benign mesenchymal lesion (often variants of fasciitis, or benign fatty, vascular or smooth muscle proliferations).[4][6] Interestingly, in at least one study it was felt that in many of the misdiagnosed cases, the target diagnosis could have been made with hematoxylin and eosin (H&E) stained sections and a limited range of immunohistochemical stains, without recourse to highly specialised antibodies or molecular genetic techniques.[4] This suggests that in many cases the missed diagnosis was due to lack of familiarity with rare entities on the part of the pathologist, emphasising the importance of experience and sub-specialty training over “high-tech” approaches.

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2.6.1.3 Effect of altered diagnosis

Delayed or incorrect diagnosis can lead to inappropriate or unnecessary surgery, chemo- or radiotherapy, or withholding of potentially life-saving therapy. Even if a diagnosis of sarcoma is correct, failure to recognise a particular tumour sub-type may preclude the employment of specific targeted therapies, and errors in grading or risk stratification may lead to more or less vigorous therapy than would otherwise have been recommended (such as whether or not to administer adjuvant treatment). In the case of aggressive tumours, even relatively short delays in accurate diagnosis can impact on patient survival.[2]

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2.6.1.4 Access to expert review/second opinions

Timely expert review is, therefore, in the best interests of the patient, but many pathologists are faced with questions over how, and to whom, these cases should be referred. Sending cases to outside institutions incurs a cost for both the referring and the receiving laboratory, and these costs are poorly accounted for, if at all. Currently, expert review of diagnostic material is not funded in the Medicare Benefits Schedule, and whilst many experts choose not to charge a fee for these referrals, institutions are increasingly demanding a fee – a cost which the referring laboratories cannot meet and which is therefore often passed on to the patient. Yet failure to obtain a timely correct diagnosis can result in unnecessary and inappropriate treatment, which in drug costs alone may be far more expensive than the pathologist's review.

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2.6.2 Evidence summary and recommendations

Evidence summary	Level	References
Expert review of bone and soft tissue tumours (BSTTs) diagnosed in non-specialist centres results in changes to the diagnosis and/or grading in a significant proportion of cases.	IV	[4], [1], [6], [2], [3], [5], [7]

Evidence-based recommendation	Grade
Whenever a primary diagnosis of bone or soft tissue sarcoma is made outside the context of a specialist sarcoma unit, wherever possible, referral to an expert pathologist (within a specialist sarcoma unit) for review of the diagnosis and grade should be undertaken before definitive management is instituted.	**D**

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2.7 Referral to specialist centre

Contents

2.7.1 Does referral to a specialist centre improve outcomes in BSTTs?

2.7.1.1 Introduction

It is estimated that a busy general practitioner will only see one to two patients with sarcoma in their clinical practice lifetime.[1][2][3]. National registries also reveal that a general orthopaedic surgeon can expect to see less than one patient with a primary bone tumour every three years.[4][5] Figures do not exist for the rates of sarcoma patients seen initially by other types of surgeon.

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2.7.1.2 Referral to specialist centres

As it will never be possible to conduct a randomised trial on this topic evidence can only be gained from analysis of series of patients treated within and outside specialist centres. This leads to significant bias in the cases reported as those patients with a good prognosis (for example a patient with a superficial tumour that is readily widely excised) are often not referred whereas those with complex treatment requirements or suspected poorer prognosis are.[6] However, even with these caveats published series consistently report that outcomes are worse when treatment is initiated in non-specialist centres.[5][7][8][9][10][11][12] Unfortunately, current estimates are that up to half of all patients with soft-tissue sarcoma (STS) are managed outside specialist centres.[1]

As sarcomas are rare, but benign soft tissue tumours are very common, surgery is often undertaken with a plan to perform enucleation or marginal excision. This usually occurs prior to any imaging or biopsy.[13][14][15] These procedures have come to be known as “unplanned surgery”.[16] There is residual tumour found at re-excision in 39-68% of these patients.[17][18][19][20] Re-excision is often a more complex and complicated procedure and the chance for optimal treatment may have been lost by unplanned surgery.[2][21][22][23][24][25] Reported local recurrence rates after unplanned surgery are in the range of 60 to 90%.[16][26][6][27][28] There is also evidence that disease-specific survival is higher in patients treated in specialist centres.[29][30][2][10][6][18]

Reported series often only consider a few of the possible outcomes of non-referral for specialist treatment. These include the effect of delayed diagnosis, the need for repeated procedures and ultimately the effects on local and distant recurrence.

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2.7.2 Evidence summary and recommendations

Evidence summary	Level	References
The rate of preoperative diagnosis in non-specialist centres ranges from 17-60%. This greatly increases the chances of incomplete resection.	IV	[13], [14], [15], [31]
When biopsies are performed in non-specialist units the errors in diagnosis, non-representative samples and biopsy site complications resulting in alterations in treatment or outcome, have been shown to be between 2–12 times greater than when the biopsy is performed in a specialist centre. Referral of patients to specialist centres results in less unplanned surgery and fewer biopsy-related complications.	IV	[5], [7], [8], [9], [10], [11], [12], [31]
The rates of positive excision margins in patients treated in non-specialist centres are often reported to be as high as 67-93%. Specialist centres generally report rates below 35%.	IV	[13], [14], [21], [5], [15], [4], [22], [16], [31]
Reoperation reveals residual disease in 39-68% of patients referred after their	III-2,	[10], [4], [15],

Evidence summary	Level	References
primary excision. Current imaging modalities are unable to reliably predict the presence of residual microscopic disease.	IV	[17], [18], [19], [20]
Reoperation becomes increasingly complex due to inappropriately placed incisions, contamination of uninvolved tissue planes and wound complications. The costs associated with treatment are significantly increased.	IV	[17], [21], [23], [2], [24], [22], [25], [19]
Treatment recommendations by the referring physician have been reported to cause anxiety and confusion as they agree with the recommendation of specialists on less than 50% of occasions.	IV	[17]
Local recurrence rates are higher following incomplete primary excision. Rates in non-specialist units are generally two to four times higher than those achieved in specialist centres.	III-2, IV	[27], [23], [18], [28], [13], [29], [7], [2], [19], [26]
Disease-specific survival is greater in patients treated in specialist centres.	III-2, IV	[18], [2], [6], [15], [29], [10], [30], [32]

Evidence-based recommendation	Grade
Patients with suspected sarcoma to be referred to a specialist sarcoma unit prior to diagnosis in order to reduce the rates of incomplete excision, reoperation, local recurrence and to improve survival.	**C**

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2.7.3 Issues requiring more clinical research study

- What are the economic implications of referral and non-referral for specialist care?

No comment pages found

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2.7.4 References

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2.8 Adjuvant systemic therapy

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2.8.1 What is the role for adjuvant systemic therapy for adults with BSTT?

2.8.1.1 Introduction

For many years surgery has been the primary treatment modality of patients with apparently localised bone and soft tissue sarcoma. Evidence has emerged of improved outcomes when sarcoma care is concentrated in referral centres specialising in these rare tumours. [1] Multidisciplinary teams including surgeons, pathologists, medical and radiation oncologists, and imaging experts have evolved in these specialist centres and commonly paediatric and AYA (Adolescent and Young Adult) oncologists, and psychosocial services are included. These specialist centres are increasingly engaged in clinical research including familial and molecular investigations, clinical trials and supportive care studies.

Chemotherapy is now playing an increasing role in the management of high grade localised sarcomas, not only as adjuvant therapy after surgical resection, but also as initial therapy (neoadjuvant) for large high-grade sarcomas in which radical surgery and/or radiation treatment is contraindicated. Several new drugs have been found to be active in sarcomas of different types, and the integration of these agents into care is the subject of current investigation. The range of sarcoma types in which chemotherapy is sometimes effective has increased and is not restricted to sarcomas diagnosed in children.

Chemotherapy can be considered either as systemic adjuvant treatment with the primary goal of treating microscopic disease at the time of initial presentation, or as a complement to local treatment by surgery or radiation. In the latter setting, the goal of chemotherapy is to ‘downstage’ the tumour enabling surgery or radiation to achieve local disease control sometimes with reduced morbidity. Tumour shrinkage or percentage necrosis after pre-operative chemotherapy may also provide important prognostic information, enabling informed treatment decisions after completion of local treatment.

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2.8.1.2 Sarcoma types

Traditionally sarcomas are divided into those arising in bone or soft tissues. This subdivision is now better informed by immune-histochemical and molecular analysis, and these studies will likely guide treatment selection in the future. Some literature considers sarcomas by their primary site and then by histological type. Commonly the outcomes of children with sarcomas are considered separately from the same histological types in older people.

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2.8.1.2.1 Bone sarcomas

The classification of bone sarcomas used most commonly in reports of treatment trials is the following:

- Osteosarcoma
- Ewings sarcoma
- Chondrosarcoma
- Malignant fibrous histiocytoma
- Spindle cell sarcomas

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2.8.1.2.2 Soft tissue sarcomas

The classification of soft tissue sarcomas used most commonly in reports of treatment trials is the following:

- Soft tissue sarcomas
- Embryonal rhabdosarcoma

- Synovial sarcoma
- Leiomyosarcoma
- Malignant fibrous histiocytoma (now undifferentiated pleomorphic sarcoma)
- Myxoid liposarcoma
- Liposarcoma

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2.8.2 Evidence summary and recommendations

Bone sarcomas

Osteosarcoma

Evidence summary	Level	References
In general chemotherapy is administered before and after surgery, but formal proof is lacking that pre-operative chemotherapy predicts survival.	II	[2]
The extent of histological response to pre-operative chemotherapy predicts survival.	II	[2]
Altering post-operative chemotherapy in poor responders to pre-operative chemotherapy has not been shown to improve outcomes. Ifosfamide and etoposide are active drugs in osteosarcoma, but their individual or combined contribution to outcomes compared to cisplatin, doxorubicin and high dose methotrexate regimens is not established.	II	[3]
Intra-arterial chemotherapy compared to intravenous administration has not been shown to improve outcome.	II	[2]

Evidence-based recommendation	Grade
Curative treatment of high-grade osteosarcoma comprises chemotherapy and surgery.	**B**

Evidence-based recommendation	Grade
Pre-operative chemotherapy for high-grade osteosarcoma including cisplatin, doxorubicin and in selected patients high-dose methotrexate, improves outcomes compared to regimens omitting high-dose methotrexate.	**C**

Malignant fibrous histiocytoma of bone

Evidence summary	Level	References
Doxorubicin and cisplatin pre-operative chemotherapy caused a good pathologic response (>90% necrosis) in 42% of assessable patients. Those with a good pathologic response had longer survival times and time to disease progression than did those with a poor response.	IV	[4]

Evidence-based recommendation	Grade
As for osteosarcoma, doxorubicin and cisplatin are indicated for malignant fibrous histiocytoma of bone.	**D**

High-grade spindle cell sarcomas of bone other than osteosarcoma or malignant fibrous histiocytoma

Evidence summary	Level	References
Pre-operative doxorubicin and cisplatin prior to resection in twenty patients caused a good histological response in two specimens.	IV	[5]

Evidence-based recommendation	Grade
As for osteosarcoma, doxorubicin and cisplatin are indicated for high-grade spindle cell sarcomas of bone and malignant fibrous histiocytoma.	**D**

Ewings sarcoma

Evidence summary	Level	References
All current trials of treatment employ pre-operative chemotherapy for three to six cycles followed by local therapy by surgery and/or radiotherapy to the primary site and this approach achieves five year-survival rates of 60% plus in those with localised disease compared to historical survival rates of 10% with surgery or radiotherapy alone.	II	[6]
Cycles of chemotherapy administered every two weeks are more effective than chemotherapy administered every three weeks.	II	[6]

Evidence-based recommendation	Grade
Curative treatment of Ewings sarcoma comprises of a combination of chemotherapy and surgery and/or radiotherapy.	**B**

Soft Tissue Sarcomas

Evidence summary	Level	References
Post-operative chemotherapy with doxorubicin in localised resectable soft tissue sarcoma reduces distant and overall recurrence OR 0.7 (95% CI 0.56-0.82; p=0. 0001). The OR for doxorubicin combined with ifosfamide was 0.56 (95% CI 0.36-0.85; p=0.01) in favour of chemotherapy.	I	[7]
Subsequent to the meta-analysis above, a large randomised controlled trial was published favouring no chemotherapy over adjuvant chemotherapy in terms of five-year overall survival rate, and demonstrated no difference between groups in terms of overall survival and relapse-free survival.	II	[8]

Evidence-based recommendation	Grade
The use of post-operative chemotherapy in adult type soft tissue sarcomas is not the current standard of care.	**D**

Evidence summary	Level	References
Three cycles of full dose pre-operative epirubicin, ifosfamide and GCSF were not inferior to five cycles.	II	[9]
Post-operative chemotherapy was associated with improved relapse free survival only in patients <30 years.	III-3	[10]

Evidence-based recommendation	Grade
The use of pre-operative chemotherapy in adult type soft tissue sarcomas is not the standard of care.	**D**

Practice point

Patients considered for chemotherapy should be referred for clinical trial participation.

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2.8.3 Issues requiring further clinical research

Future studies should focus on larger grade III and extremity sarcomas.

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2.9 Systemic therapy

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2.9.1 What is the role for systemic therapy in advanced soft-tissue sarcoma?

2.9.1.1 Introduction

Soft-tissue sarcomas comprise over fifty histologically distinct subtypes, with corresponding differences in molecular aetiology and biological behaviour.[1] The first presentation with advanced (metastatic or unresectable) disease raises the issue of the timing and types of therapeutic options.

There are three therapeutic options that may be considered. The first is watchful waiting, which may be suitable particularly for indolent and asymptomatic sarcoma subtypes, especially in an elderly or frail population. The second is consideration of local therapies, particularly radiotherapy, for symptomatic or rapidly progressive single or oligometastatic disease. Objective local control rates for radiotherapy approach 80%. Finally, consideration may be given to systemic therapy. Most (but not all) types of soft-tissue sarcoma tend to be relatively resistant to systemic therapies, with objective response rates ranging from 0-50%, depending on subtype. In no circumstance is systematic therapy for advanced or unresectable soft-tissue sarcoma considered curative, although a subset of patients may have substantial, long-term survival in this situation.[2]

Systemic therapy for advanced soft tissue sarcoma may be divided into aggressive and gentle palliation. The therapeutic decision between these two approaches usually depends on the need for rapid disease control, the state of fitness of the patient, the type of sarcoma, and the therapeutic philosophy of the patient and treating clinician. The need for rapid disease control is determined by the symptoms of the patient, and the rate and sites of progression of the tumours. Recent data suggest little difference on overall survival between doxorubicin alone or when administered with ifosfamide, when administered in first line for advanced disease.[3]

For the most common subtypes of soft-tissue sarcomas (pleomorphic high-grade undifferentiated sarcoma, leiomyosarcoma, well- or de-differentiated liposarcoma, pleomorphic liposarcoma and myxoid liposarcoma, and synovial cell sarcoma), the major therapeutic options with Australian regulatory approval for soft-tissue sarcoma are based on anthracycline and alkylating agents, gemcitabine with taxanes or dacarbazine, or dacarbazine alone. Gemcitabine and docetaxel may be superior to single agent doxorubicin for uterine leiomyosarcoma.[4] It is notable that doxorubicin and alkylators appear to have significant dose-response relationships, which may influence the choice of agent depending on the need for disease control.

Newer agents are emerging with clinical activity in advanced soft-tissue sarcomas, such as trabectedin and pazopanib. Trabectedin is not approved by the Therapeutic Goods Administration for this indication. Pazopanib has recently been recommended for listing by the Pharmaceutical Benefits Advisory Committee onto the Pharmaceutical Benefits Scheme.

For a specific subset of sarcomas, including dermatofibrosarcoma protuberans, alveolar soft-part sarcoma, perivascular epithelioid cell tumor (PEComa), and to a lesser extent for angiosarcoma and desmoid tumours, evidence for the selective activity of various targeted and non-targeted therapies may be considered.

Given the difficulties in making clear pathologic diagnoses, the absence of level I or II evidence for most therapeutic recommendations, and the complexities of expert multidisciplinary care, patients with soft-tissue sarcoma should be referred to a multidisciplinary service with dedicated interests in the management of sarcomas.

Where there is no high level evidence for standard practice, then entering patients into clinical trials should be considered.

2.9.1.2 Specific soft-tissue sarcoma subtypes

The development of kinase inhibitor therapy (KIT) and other kinase-directed inhibitors for gastrointestinal stromal tumours (GIST) have sparked a strong effort to identify similar specific molecular drivers for other sarcoma subtypes. GISTs will not be discussed as part of these guidelines, but it is important to note that the differential diagnosis of GIST should be considered carefully in any patient with an intra-abdominal soft tissue sarcomas (STS) given the treatment implications.

Apart from GIST, there have been other noted examples of molecularly-targeted therapies that should be considered for selected subtypes. **Dermatofibrosarcoma protuberans (DFSP)** have a characteristic translocation (t17:22) that results in the creation of a fusion oncogene between COL1A1 and PDGFB, which results in constitutively activated PDGF. These tumours are highly sensitive to PDGF inhibition with imatinib, which is registered/reimbursed for inoperable DFSP in Australia.[5]

Activity has also been noted in the following sarcoma subtypes with molecularly-targeted therapies. **Malignant perivascular epithelioid cell tumors (PEComas)** are often associated with the loss of tuberous sclerosis complex (TSC1/TSC2 tumour supressors), with clear activity noted with mammalian target of rapamycin (mTOR) inhibitors.[6]

Inflammatory myofibroblastic tumours are associated with transolcations of anaplastic lymphoma kinase (ALK) in approximately 50% of cases; activity has been reported with the ALK inhibitor crizotinib.[7]

Alveolar soft-part sarcoma (ASPS) are highly vascular tumours that typically affect adolescents and young adults.Clear activity has been noted in patients treated with VEGF-directed tyrosine kinase inhibitors including sunitinib and cediranib. Of note, in a recent large phase II trial with cediranib, 15 of 43 patients achieved a partial response (35%) with a disease control rate at 24 weeks of 84%.[8]

Desmoid tumours (also known as aggressive fibromatosis or desmoid type fibromatosis) have a highly variable natural history, with some patients having prolonged stable disease or even spontaneous regressions. Although they are not at risk of metastasising, local invasion into vital structures can cause significant morbidity and may be fatal. Intra-abdominal desmoids tumours in particular, are invariably infiltrative into surrounding mesenteric structures, making R0 surgery very difficult to achieve. The clinical algorithm for patient management is therefore complex, and should be individualised after taking into account the above factors. As a general principle, a watchful waiting approach is preferred. Systemic therapies should be reserved for patients with clear disease progression on serial assessments, or in patients with clear symptoms from their disease and for whom localised measures such as radiotherapy or surgery have also been considered. Systemic therapy options include cytotoxic and non-cytotoxic agents, with a general approach to consider a stepwise progression from less toxic non-cytotoxic agents to cytotoxics.[9][10][11][12][13][14][15]

Angiosarcomas, although not characterised molecularly, need to be considered as a distinctive soft tissue subtype, and treated accordingly.

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2.9.2 Evidence summary and recommendations

2.9.2.1 Systemic approaches to common soft-tissue sarcomas

First-line

Evidence summary	Level	References
Doxorubicin, alone or in combination with ifosfamide is standard first-line treatment. Although the response rate to doxorubicin as a single agent is lower than to the combination, the toxicity of the combination is greater and there is to date no evidence of a difference in overall survival for patients treated with the combination.	I, II, IV	[16], [17], [18], [19], [3]
For patients in whom doxorubicin is considered inappropriate (for example, for patients who have received doxorubicin as part of adjuvant or neoadjuvant therapy, or for patients who have cardiac dysfunction, or who have glucose-6-phosphate dehydrogenase deficiency), ifosfamide as a single agent has the second highest objective response rate.	II, IV	[20], [21]
For patients with uterine leiomyosarcoma, the combination of docetaxel and gemcitabine may be considered in first-line.	III-1, IV	[22], [23], [4]

Evidence-based recommendation	Grade
There is no evidence to support combination chemotherapy regimens over sequential single agent regimens in the first-line treatment of advanced soft-tissue sarcomas.	**B**

Second-line and third-line

Evidence summary	Level	References
For patients who have not received ifosfamide as first-line, single agent ifosfamide may be considered.	I, II	[21], [24]
For patients with myxoid liposarcoma or leiomyosarcoma, consideration may be given to trabectedin.*	II, III-2, IV	[25], [26], [27], [28]

Evidence summary	Level	References
For patients who have been exposed to both doxorubicin and ifosfamide, dacarbazine is considered the next most active approved agent. If aggressive combination therapy is indicated, the combination of dacarbazine and gemcitabine has demonstrated a survival benefit compared to dacarbazine alone.	II	[29]
The antiangiogenic agent, pazopanib, was superior to placebo in progression-free but not overall survival, in patients with advanced soft tissue sarcomas (excluding GIST and adipocytic tumours) who have received prior chemotherapy.	II	[30]

*Trabectedin is not approved in Australia for soft-tissue sarcoma.

Evidence-based recommendation	Grade
Single agent ifosfamide can be considered as second-line treatment for patients who have not received ifosfamide as first-line.	**B**

Evidence-based recommendation	Grade
Dacarbazine with or without gemcitabine is reasonable third-line therapy after exposure to doxorubicin and ifosfamide in advanced soft tissue sarcoma.	**B**

Systemic approaches to other selected soft-tissue sarcomas

Evidence summary	Level	References
Hormonal agents (anti-oestrogens such as tamoxifen), alone or in combination with nonsteroidal anti-inflammatory drugs (sulindac) have shown some activity in treating Desmoid tumours. Molecularly-targeted agents including imatinib* and sorafenib* have been assessed in single-arm, non-randomised phase II trials, with some level of activity. If other options have failed or are there is a need for a more aggressive approach, cytotoxic options include those that are less toxic (combination of methotrexate and vinblastine or vinorelbine) or more toxic (doxorubicin by prolonged intravenous infusion, or ideally delivered in its liposomal formulation) have shown some levels of activity. However, all of these results must be taken in context, given the highly variable natural history of disease and lack of control arm comparisons with any of these studies	III-2, IV	[9], [10], [11], [12], [13], [14], [15]

Evidence summary	Level	References
Paclitaxel (administered weekly) and liposomal doxorubicin both have activity in angiosarcomas. Although primary angiosarcomas, which often arise in the head and neck, are more chemo-sensitive than those that are radiation-associated, systemic therapy should be considered in all of these patients given the palliation that can be offered by these agents.	IV	[31]

*Imatinib and sorafenib are not approved or reimbursed for this indication in Australia.

Evidence-based recommendation	Grade
Systemic therapy with paclitaxel is reasonable in all patients with angiosarcoma, given the palliation that can be offered by these agents.	**D**

Practice point
Clinical trial participation should be considered for patients with soft tissue sarcomas.

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2.9.3 References

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2.10 Radiotherapy in STS

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2.10.1 What is the evidence for radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage?

2.10.1.1 Introduction

Modern management of limb and extremity soft tissue sarcoma (STS) typically consists of a combination of limb preserving surgery and radiotherapy (RT). Pre-operative or post-operative RT, intraoperative or perioperative brachytherapy with or without external beam radiotherapy (EBRT) have been used and reported by investigators from various institutions.

2.10.1.2 Evidence of radiotherapy in terms of local recurrence

Post-operative RT improves local control in combination with limb preserving surgery in patients with high or low grade extremity STS who had negative or marginal margins.[1] A local control rate in excess of 90% has been reported.

In the cases of intralesional margin, post-operative RT has been shown to improve local control (5yr local control 28% vs. 62%). However, the control rate remains inferior to cases in which a wide margin can be achieved.[2]

One randomised trial and several retrospective reports comparing pre-operative RT and post-operative RT have reported similar local control.[3]

Post-operative brachytherapy has been shown to improve local control in high grade STS after complete resection in a randomised controlled trial.[4][5][6] Although the local control benefit was not shown in low grade STS, this subset analysis was limited to 22 and 23 patients in each arm.

A French retrospective study evaluating altered fractionation schedule in the post operative setting reported no improvement in local control compared to conventional fractionated radiotherapy of 1.8-2Gy fractions.[7]

There is no evidence that the addition of radiosensitizer to post-operative radiotherapy improves local control.[8]

A prospective trial by Pisters et al.[9] in 2007 of 88 patients with T1 STS showed that a policy of R0 surgery alone (reserving post-operative radiotherapy for positive margins only) resulted in 5- and 10-year local recurrence rates of 14% and 16.2% for the entire cohort. The corresponding rates in the R0 surgery alone arm was 7.9% and 10.6%.

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2.10.1.3 Evidence for radiotherapy in terms of survival

Randomised studies for post-operative radiotherapy or brachytherapy following limb sparing surgery did not demonstrate any survival benefit. However, it is unclear if the sample sizes in these earlier trials were adequately powered to detect a difference in survival outcomes.

There is, however, level III-2 evidence from a SEER analysis by Koshy et al, 2010[10] that a statistically significant improvement in overall survival (OS) in patients with high grade extremity STS who received radiotherapy (three year OS 73% versus 63%) was demonstrated.

This was confirmed in another SEER analysis by Schreiber et al, 2012[11] which reported an improved OS and disease specific survival (DSS) for patients with tumours >5cm who had post-operative radiotherapy after limb sparing surgery.

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2.10.1.4 Evidence for radiotherapy in terms of limb salvage

There is level II evidence that the DSS and OS were equivalent in patients with high grade extremity STS who had limb sparing surgery with post-operative radiotherapy compared with those managed with amputation.[12]

Majority of these patients has excellent local control and acceptable functional outcome.

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2.10.2 Evidence summary and recommendations

Evidence summary	Level	References
Adjuvant radiotherapy improves local control in combination with limb preserving surgery in patients with high or low-grade extremity STS who had negative or marginal margins.	II	[1]
Adjuvant radiotherapy improves local control in the cases of intralesional margin. However, the control rate remains inferior to cases in which a wide margin can be achieved.	IV	[2]
Local control was similar in both the pre-operative RT and post-operative RT group.	II	[3]

Evidence summary	Level	References
Radiotherapy demonstrated improvement in overall survival only in patients with high grade extremity STS.	III-2	[10], [11]

Evidence-based recommendation	Grade
All patients with large, localised, high-grade extremity soft tissue tumours should be offered radiotherapy.	**B**

Evidence summary	Level	References
R0 surgery alone demonstrated acceptable local control and sarcoma specific survival rates in selected patients with T1 extremity STS.	IV	[9]

Evidence-based recommendation	Grade
Omission of radiotherapy may be considered in select patients with small, superficial, extremity soft tissue tumours.	**D**

Practice point
Radiotherapy does not compensate for inadequate surgery.

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2.11 Pre-operative radiotherapy

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2.11.1 What is the evidence that pre-operative radiotherapy is superior to post-operative radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage and morbidity?

2.11.1.1 Introduction

The optimal sequencing of radiotherapy and limb-sparing surgery in extremity soft tissue sarcoma (ESTS) is unclear. Following the landmark randomised trial by Rosenberg,[1] surgery followed by post-operative radiotherapy (RT) became, a widely practiced approach in localised resectable ESTS.

Subsequent interest in utilising radiotherapy in the pre-operative setting has been reported in multiple retrospective series. To date, there has only been one randomised controlled trial comparing pre-operative and post-operative radiotherapy in ESTS, and one systematic review/meta-analysis including the above randomised and four retrospective cohort studies. These are briefly summarised below. The majority of literature, in fact, lies in single-institutional case series.

O'Sullivan et al[2] randomised 190 patients to pre-operative radiotherapy (50Gy) versus post-operative radiotherapy (66-70Gy), with major wound complications being the primary endpoint. Patients whom received pre-operative radiotherapy had a significantly higher rate of major wound complications compared with patients receiving post-operative radiotherapy (35% versus 17%; p=0.01), with the highest rates of complications seen in the thigh. At a median follow-up of 3.3 years, local control was similar in both groups (p=0.7119). A difference in overall survival, was demonstrated favouring the pre-operative arm (p=0.0481), however the study was not powered to detect a difference in this secondary endpoint.

An update to this trial at a median follow-up of 6.9 years was presented in abstract form and confirmed ongoing equivalence of local control between the two arms (93% versus 92%), and similar overall survival (73% versus 67%; p=0.48).

Longer term functional outcomes for this trial were reported at two years by Davis et al,[3] and included 73 and 56 patients in the pre-operative and post-operative arms, respectively. A greater proportion of patients in the post-operative arm had grade 2 or greater subcutaneous fibrosis, edema and joint stiffness, however these differences did not reach statistical significance.

A systematic review/meta-analysis, included a total of 1,098 patients and reported moderate heterogeneity between studies as well as likely publication bias. It concluded there may be lower risk of local recurrence with pre-operative radiotherapy, with no likely detriment in overall survival.

A retrospective analysis conducted using the National Oncology Database,[4] included a total of 821 patients from multiple institutions across the United States, reported a statistically improved overall survival (OS) and cause specific survival (CSS) in the pre-operative RT group compared with post–operative RT group (HR =0.72, 95% CI 0.56-0.91, p<0.01, and HR =0.64, 95% CI 0.46-0.88, p<0.01, respectively). Pre-operative RT was also associated with a significantly reduced risk of local and distant relapse compared with post-operaive RT, with a five year local failure-free survival of 93% and 87%, respectively (p<0.05) and five year distant metastases-free survival of 89% and 77%, respectively (p<0.001).

Of note, there are three retrospective studies that have compared the outcome of pre-operative RT versus post-operative RT and found no difference in local control or CSS.

Although the analysis by Sampath et al[4] is the largest retrospective analysis comparing the outcomes of pre-operative and post-operative RT, it is still subjected to all the inherent limitations of a retrospective database study. Nevertheless, it suggests the need for additional clinical trials to examine the impact of RT sequence on clinical outcomes.

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2.11.2 Evidence summary and recommendations

Evidence summary	Level	References
There is no significant difference in local control or survival between pre-operative and post-operative radiotherapy in localised resectable extremity soft tissue sarcoma (ESTS).	II, III-2	[2], [5]
Pre-operative radiotherapy increases the rate of wound complications, following limb-sparing surgery for extremity soft tissue sarcoma (ESTS).	II	[2]
Post-operative radiotherapy may increase the rate of long-term radiation toxicity including subcutaneous fibrosis, edema and joint stiffness.	II	[6]

Evidence-based recommendation	Grade
The timing of radiotherapy needs to be individualised dependent upon resection and reconstructive considerations.	**B**

Practice point

Pre-operative radiotherapy may be the preferred approach in certain situations such as:

A tumour of borderline resectability, and pre-operative radiotherapy may render it resectable.

Radiosensitive histology (eg., myxoid liposarcoma), where tumour downstaging may be advantageous.

Where adjacent critical structures (eg., brachial plexus) may limit the total dose of post-operative radiotherapy.

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2.11.3 References

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2.12 Radiotherapy in truncal sarcomas

Contents

2.12.1 What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in truncal sarcomas?

2.12.1.1 Introduction

Truncal sarcomas are rare, accounting for about 6% of all soft tissue sarcomas (STS) and about half of all malignant tumours arising on the chest wall. The clinical behaviour of chest wall sarcomas is similar to extremity sarcomas. Thus, they should be treated similarly to extremity sarcomas.[1] [2]

Because of the rarity of this type of sarcoma, data concerning treatment and results are sparse. In the largest single institution study by Memorial Sloan-Kettering Cancer Center (MSKCC) spanning over a period of forty years looking at 189 patients, the authors reported overall five year survival was 66%, with low grade sarcomas showing 90% survival as compared to 49% with high grade sarcomas. Local recurrence was more common in high grade tumours even after resection, and adjuvant treatment was recommended. However with low grade tumours, resection alone provided good survival at 90%. The most common tumours seen were desmoids, liposarcoma, rhabdomyosarcoma and Fibrosarcoma. Survival was similar to that of patients with sarcomas of the extremities.

2.12.1.2 Rationale for Radiotherapy

Given the similarity to extremity sarcomas in terms of local recurrence and metastases, most reports suggest treating them as for extremity sarcomas.

Radiation therapy is a well-established modality in Sarcoma of the extremities along with surgery to achieve good local control of up to 90%, especially in high grade sarcomas. There are many institutional reports of high local control by adding radiation therapy to surgery.

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2.12.1.3 Evidence for Local control benefit with radiotherapy in addition to surgery

A systematic review in 2003 by the Swedish group concluded that, “there is strong evidence that adjuvant radiotherapy improved local control in combination with surgery in the treatment of STS of extremities and trunk in patients with negative, marginal or minimal microscopic positive surgical margins. A local control rate of 90% has been achieved”[3]

A more recent study looked at twenty year data of 1093 sarcoma patients, 151 of whom were truncal sarcomas and concluded that “adjuvant radiotherapy (RT) effectively prevents local recurrence in soft tissue sarcoma and the effect was most pronounced in deep seated high grade tumours, even when removed with a wide surgical margins”[4]

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2.12.1.4 Pre-operative versus post-operative radiotherapy

As with extremity sarcomas, there are potential benefits with pre-operative RT compared with post-operative RT such as:

- The main advantage of pre-operative RT is that the gross tumour volume can be precisely defined for radiation treatment planning, allowing accurate targeting of the radiation volume around the tumour.
- The tumour itself can act to displace small bowel from the high-dose radiation treatment volume, resulting in safer and less toxic treatment.
- Higher RT doses can be delivered to the actual tumor field, since bowel adhesions to tumour are less likely compared to the post-operative setting.
- The risk of intraperitoneal tumour dissemination at the time of the operation may be reduced by pre-operative RT.
- Radiation is considered to be biologically more effective in the pre-operative setting.
- It is possible that an initially unresectable tumour may be converted to one that is potentially resectable for cure.

Potential downsides of pre-operative radiation therapy include delay in wound healing and requirement of surgery to treat this complication.

Post-operative radiation therapy on the other hand allows detailed evaluation of pathology (grade, margins, etc) but disadvantages include higher doses or radiation therapy, larger volumes of radiation therapy, maybe technically difficult trying to cover larger volumes and finally potential late adverse events including fibrosis and bone fractures which may impact on quality of life.

With lack of randomised controlled trials to guide us when dealing with this cohort (truncal sarcomas) individualised multidisciplinary discussion of the benefits of the choice and order of surgery or radiotherapy may be appropriate.

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2.12.1.5 Newer radiotherapy techniques

There is some evidence that newer RT techniques such as intraoperative electron beam therapy (IORT) may be beneficial, but this is usually confined to few centres worldwide and not available in Australia. There is some promise with the use of intensity modulated radiation therapy (IMRT) in truncal sarcomas but still in early stages and may take some time for results to come.

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2.12.2 Evidence summary and recommendations

Evidence summary	Level	References
	III-2, IV	[3], [4]

Evidence summary	Level	References
In patients presenting with non-metastatic truncal sarcomas, improved local control is seen with adding radiation therapy to surgery. Pre-operative radiotherapy is preferable. Post-operative radiotherapy (in the absence of spacing devices) is associated with significant toxicity. Evidence regarding radiotherapy benefit in improving overall survival is not clear.		

Evidence-based recommendation	Grade
In patients with non-metastatic truncal sarcomas, adding radiotherapy to surgery is appropriate to further improve local control. When offered, pre-operative radiotherapy is preferable to post-operative radiotherapy.	**C**

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2.12.3 Issues requiring more clinical research study

A number of gaps in the evidence have been identified. These include:

• Clear definition of truncal sarcomas - sarcomas of the body (external) excluding limbs and head, with regular audit of outcomes.

• Nationally run randomised controlled trial looking into pre-operative versus post-operative RT in truncal sarcomas will answer questions more definitively regarding concerns related to toxicity.

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2.12.4 References

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2.13 Radiotherapy in retroperitoneal sarcomas

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2.13.1 What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in retroperitoneal sarcomas?

2.13.1.1 Introduction

Retroperitoneal Sarcomas (RPS) are relatively uncommon, constituting 10-15% of all Soft Tissue Sarcomas (STS). Patients usually present in their fifties, although the age range can be broad. Both males and females are equally affected. The most common histologic types of RPS are liposarcomas, leiomyosarcomas and pleomorphic undifferentiated sarcomas. RPS typically produce few symptoms until they are large enough to compress or invade surrounding structures. Most cases come to attention as an incidentally discovered abdominal mass in an asymptomatic or minimally symptomatic patient. Most tumours are already large at presentation (median size 15cm).

2.13.1.2 Rationale for adding Radiotherapy

Surgical resection has traditionally been the only potentially curative treatment of localised RPS. However, in contrast to Extremity STS where the most common site of first recurrence is a distant site, the primary pattern of failure after resection of a RPS is local. Five year local recurrence rates after complete resection of a RPS is around 50% and local recurrence is the site of first failure in 90% of cases. These high relapse rates have prompted investigation of combined modality approaches such as radiation therapy.

Unfortunately, with RPS being an “Orphan Disease” there are no randomised trials of surgery with and without External beam radiation therapy (EBRT). There was one trial Z9031 initiated by the American College of Surgeons Oncology Group (ASCOG) randomising to preoperative radiotherapy (RT) vs Surgery alone. This closed prematurely due to slow patient accrual. At the time of writing, the European Organisation for Research and Treatment of Cancer (EORTC) protocol 62092 is preparing to accrue patients for a phase III randomised controlled trial comparing preoperative RT plus surgery vs surgery alone for patients with RPS. However, the results of this study will not be available for many years to come.

There are many retrospective studies, mainly institutional reports which have shown improved local control benefit. Two large studies [1][2] have shown that adjuvant RT improves local recurrence free survival significantly. Recent large population based multi-institutional studies such as SEER database analysis which have looked at overall survival benefit have however been conflicting. A smaller SEER analyisis[3] showed no survival benefit, where as an analysis with larger number showed a survival benefit.[4] Another SEER analysis[5] showed survival benefit in malignant fibrous histiocytoma (MFH) subgroup only.

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2.13.1.3 Pre-operative versus post-operative radiotherapy

Although the studies had a mix of pre-operative or post-operative RT, there are benefits with pre-operative RT versus post-operative radiotherapy such as:

- The main advantage of pre-operative RT is that the gross tumour volume can be precisely defined for radiation treatment planning, allowing accurate targeting of the radiation volume around the tumour.
- The tumour itself can act to displace small bowel from the high-dose radiation treatment volume, resulting in safer and less toxic treatment.
- Higher RT doses can be delivered to the actual tumour field, since bowel adhesions to tumour are less likely compared to the post-operative setting.
- The risk of intraperitoneal tumour dissemination at the time of the operation may be reduced by pre-operative RT.
- Radiation is considered to be biologically more effective in the pre-operative setting.
- It is possible that an initially unresectable tumour may be converted to one that is potentially resectable for cure.

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2.13.1.4 Newer Radiotherapy techniques

There is some evidence that newer RT techniques such as Intraoperative Electron beam therapy (IORT) may be beneficial, but this is usually confined to few centres worldwide and not available in Australia. There is some promise with the use of Intensity modulated radiation therapy (IMRT) in RPS, but still in early stages and may take some time for results to come.

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2.13.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients presenting with non metastatic retroperitoneal sarcomas, improved local control and local recurrence free survival benefit is seen with pre-operative or post-operative radiotherapy. Pre-operative radiotherapy is preferable. Post-operative radiotherapy (in the absence of spacing devices) is associated with significant toxicity.	III-2, IV	[6], [2], [1]
Evidence regarding radiotherapy benefit in improving overall survival is not clear.	III-2	[3], [4], [5]

Evidence-based recommendation	Grade
In patients with non-metastatic retroperitoneal sarcomas, adding radiotherapy to surgery is appropriate to further improve local control. When offered, pre-operative radiotherapy is preferable to post-operative radiotherapy.	**C**

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2.13.3 Issues requiring more clinical research study

A number of gaps in the evidence have been identified. These include:

• Randomised Controlled trial comparing pre-operative RT followed by surgery versus surgery alone in patients presenting with non-metastatic retroperitoneal sarcoma.

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2.13.4 References

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2.14 Comparison: Types of radiotherapy

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2.14.1 What are the indications for IMRT, brachytherapy, intraoperative radiotherapy (IORT), extra-corporeal radiotherapy and particle therapy in the management of BSTTs?

2.14.1.1 Introduction

The standard adjuvant radiotherapy, whether used pre-operatively or post-operatively in the management of sarcomas tends to be 3-D Conformal Radiotherapy (3-DCRT). However, there are additional older (brachytherapy) and newer (IMRT, particle therapy etc) methods of delivering the radiation that may have advantages in specific situations.

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2.14.1.2 Brachytherapy

There is definite evidence that adjuvant brachytherapy improves local control over surgery alone in the management of high grade soft tissue sarcomas of the extremity and superficial trunk.[1][2] The enhancement of local control however does not extend to low grade tumours.[1][3][2] The addition of brachytherapy does not seem to increase morbidity significantly over surgery alone, though a higher wound complication rate is noted,[4] as with pre-operative radiation. Brachytherapy may have a higher early wound complication rate when compared with External Beam Radiation alone.[5]

Brachytherapy has been used as a “boost” in retroperitoneal sarcomas (RPS), intraoperatively, either with pre-operative[6] or post-operative[7] external beam radiation. An enhancement of local control has been suggested in several case series. A small randomised study showed benefit with use of HDR–IORT.[8] However no advantage with HDR–IORT is seen in local control or overall survival at 10 years when combined with preoperative radiotherapy. [9]

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2.14.1.3 Intra-operative radiotherapy (IORT)

IORT is used as a method to boost radiation doses to areas of subclinical and microscopic disease positivity identified during time of the surgery. The advantages are it allows high doses to be delivered to areas of clinical concern while sparing normal tissue. IORT can be delivered with an external beam method,[10] using electrons or with high dose rate brachytherapy (HDR).[7] A small randomised study of 35 patients compared post-operative external beam radiation alone in one arm with IORT boost followed by smaller doses of external radiation for patients with retroperitoneal sarcomas. Lower local recurrences (6 out of 15) were reported with IORT compared with post-operative external radiation alone (16 out of 20). Significantly lower radiation enteritis was noted in the IORT arm than the control arm; however a higher rate of neuropathy was reported.[8]

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2.14.1.4 Intensity modulated radiotherapy (IMRT)

IMRT or Intensity modulated radiotherapy is a radiation planning and delivery technique that is more complicated and potentially more precise than conventional methods of radiotherapy that use forward planned 3-D Conformal Radiation techniques.

IMRT has been evaluated to reduce wound complications by sparing the uninvolved tissues.[11] There are case reports of excellent local control and better sparing of normal tissue when used adjuvant with surgery[12][13][14][15] in limb and truncal sarcomas.

For retroperitoneal sarcomas there are a few plan comparison studies and case reports suggesting better dose conformity to the target and lower doses to organs at risk with IMRT technique.[16][17]

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2.14.1.5 Intraoperative extra-corporeal radiotherapy

Management of bone and soft tissue tumours (BSTTs) at times may involve resecting the diseased segment of the bone of a patient with bone or soft tissue tumour. The resected specimen can be replaced by an allograft or prosthesis. The use of Extracorporeal Radiotherapy to the bone fragment allows the patients own resected bone specimen to be use as an “autograft”.

The process involves “en bloc” wide excision of tumour, curettage and removal of tumour in theatre, than transportation of the specimen for Extracorporeal Radiation to a dose of 50Gy to 300Gy in a single fraction[18][19][20][21][22][23][24] and re-implantation in the patient, as an autograft.

There are a few case series around the world reporting generally good functional outcomes.[18][19][20][21][22][23][24] A higher complication rate, mainly infection and delayed healing is noted in some case series.[23]

Histopathological examination after Extracorporeal radiotherapy in one case series showed complete sterilization of tumour cells in all specimens examined, but viable chondrocytes capable of laying matrix.[20]

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2.14.1.6 Particle therapy

Standard radiotherapy utilises high energy X-Rays (gamma rays) or photon beams for treatment. Particle therapy is a form of external beam radiotherapy using beams of energetic protons, neutrons, or positive ions such as Carbon ions for cancer treatment. The most common type of particle therapy is proton therapy.

For protons and heavier ions, the dose increases while the particle penetrates the tissue and loses energy continuously. Hence the dose increases with increasing thickness up to the Bragg peak that occurs near the end of the particle's range. Beyond the Bragg peak, the dose drops to zero (for protons) or almost zero (for heavier ions). The perceived advantage of this energy deposition profile is that less energy is deposited into the healthy tissue surrounding the target tissue. There is no available confirmatory evidence comparing particle beam radiation with photon beam therapy (conventional radiation) in management of bone and soft tissue sarcomas. There are a number of published case series describing outcomes with proton beam[25][26][27][28] and carbon ion therapy[29][30][31][32] for bone and soft tissue tumours. A phase 2 study of patients with spinal and

paraspinal sarcomas treated with particle beam therapy after biopsy or resection had a five-year actuarial local control, recurrence-free survival, and overall survival are: 78%, 63%, and 87% respectively[33] Serizawa et al[31] from Chiba, Japan report on 24 patients with unresectable retroperitoneal sarcomas treated with Carbon ion therapy. The five year local for this group of unresectable patients is 69%, with no toxicity greater than grade 2. Scultz-Ertner[30] from Germany report 81% local control for Chordoma and 100% local control at three years for Chondrosarcoma in their experience. No grade 4/5 complications were noted.

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2.14.2 Evidence summary and recommendations

Brachytherapy

Evidence summary	Level	References
Brachytherapy improves local control over surgery alone in the management of high grade soft tissue sarcomas of the extremity and superficial trunk.	II	[1], [3]
Effect does not extend to low grade tumours.	II	[1], [3], [2]
Brachytherapy may have higher wound complication rate compared to External Beam Radiation.	III-2	[5]
Brachytherapy boost with IORT may add small benefit over post operative external radiation alone for retroperitoneal sarcomas.	II	[8]
Brachytherapy boost with IORT adds no benefit to preoperative radiation alone for retroperitoneal sarcomas.	III-2	[9]

Evidence-based recommendation	Grade
Brachytherapy (as an alternate or as a boost to external beam radiation) improves local control over surgery alone for high grade sarcomas for the limb and trunk.	**B**

Intraoperative radiotherapy (IORT)

Evidence summary	Level	References
IORT when combined with surgery and external beam radiotherapy may improve local control.	II	[8]
Other combinations and forms of delivering IORT, such as electron beam, may offer	IV	

Evidence summary	Level	References
benefit.		[7], [6], [10]

Evidence-based recommendation	Grade
IORT boost to external radiation could be considered in combination with surgery for management of retroperitoneal sarcomas.	**B**

Intensity modulated radiation therapy (IMRT)

Evidence summary	Level	References
Insufficient evidence to confirm IMRT results in lesser complications by more normal tissue sparing. Better conformity in plans and lower doses to normal tissues noted for both limb and retroperitoneal sarcoma plans.	III-2, IV	[11], [12], [14], [15]

Evidence-based recommendation	Grade
It maybe reasonable to consider IMRT for patients with retroperitoneal and extremity/truncal sarcomas as adjuvant to surgery, if resource permits, for potential advantages in reduction of radiation dose to normal tissues.	**D**

Intraoperative extra-corporeal radiotherapy

Evidence summary	Level	References
Case series from few centres around the world suggests en Bloc wide local excision, removal of tumour and reimplant of the “autograft” after a single large fraction of radiation to the resected fragment of bone is a viable option for reconstruction with satisfactory to good functional outcomes. Doses of radiation used are 50Gy to 300Gy. There appears to be complete sterilization of tumour at these dose levels.	IV	[18], [19], [20], [21], [22], [23], [24]

Evidence-based recommendation	Grade
Reconstruction using the patients own resected bone (previously bearing the sarcoma)	

Evidence-based recommendation	Grade
fragment after a large extra-corporeal dose of radiation is a possible option reported to have satisfactory to good functional outcomes.	**D**

Particle therapy

Evidence summary	Level	References
Particle beam therapy such as proton and carbon ion therapy appear to provide excellent local control in unresectable and partially resected sarcomas, particularly Chordomas, Chondrosarcomas of sacrum and skull base and retroperitoneal sarcomas. Toxicity reported appears to be low. No direct comparison between particle beam therapy and equivalent doses of photon beam therapy exists for sarcomas.	IV	[25], [26], [33], [29], [30], [31], [32], [28]

Evidence-based recommendation	Grade
Particle beam therapy appears to offer good local control with acceptable toxicity.	**D**

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2.14.3 Issues requiring more clinical research study

A number of gaps in the evidence have been identified. These include:

IORT

• Consensus / Confirmation that radiotherapy improves local control in Retroperitoneal Sarcomas.

• If above consensus/confirmation is reached, value of IORT as an additional boost to EBRT to further improve local control can be tested.

IMRT

• Comparative study of 3DCRT and IMRT for Retroperitoneal and Limb/Truncal Sarcomas to demonstrate lower normal tissue toxicity with IMRT.

Intraoperative extra-corporeal radiotherapy

• Comparative study to determine function outcome differences between use of prosthesis, bone bank allografts and extra-corporeally radiated autografts.

Particle therapy

• Study comparing particle beam therapy and photon therapy for sarcomas with local control and toxicity as end points.

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2.15 Factors influencing surgery extent

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2.15.1 What are the factors influencing the extent of surgery in BSTTs?

2.15.1.1 Introduction

The objective of surgery in the management of malignant bone and soft tissue tumours (BSTTs) is to achieve adequate oncologic margins and to provide an acceptable functional reconstruction if possible. Amputation was previously the mainstay of surgical management. This has changed due to the advancement in chemotherapy and radiotherapy, improvements in implants and bone and soft tissue reconstruction techniques, and imaging modalities that has allowed accurate assessment of the extent of the tumour and surgical margins. Limb salvage surgery is now the goal and is achievable in over 90% of patients. This is, however, technically challenging and should be performed by surgeons who are proficient in the technique in the setting of a multidisciplinary team and in a specialist tumour centre.

BSTTs are characterised by the development of a mass, which causes symptoms or signs that lead to the diagnosis of the tumour. The nature of this mass will determine the extent of surgery required to achieve lasting local control of disease.

Benign tumours may be treated by surgery alone, whereas malignant tumours (primary and secondary) often require modern multimodal care, which includes radiotherapy, chemotherapy or a combination of the two in addition to surgery. This review will be confined to the management of malignant primary tumours.

Before planning surgery the following steps are highly recommended:

- **History and examination** to determine the behaviour and characteristics of the mass, which will aid the determination of aggressiveness.
  - Any lump greater than 5 cm or deep to the deep fascia should be considered a sarcoma until proven otherwise.
  - Persistent and unremitting pain, unresponsive to oral analgesia and nocturnal in occurrence should be investigated and bone tumour excluded.
- **Local staging** of the mass with anatomic imaging including plain radiographs, computed tomography, magnetic resonance imaging, bone scans, thallium scan, positron emission tomography. Local staging allows an assessment of the anatomic location, size, relationship to important visceral, neurovascular and musculoskeletal or joint structures. This information will be important for determining the surgical margin that is best suited for local control of disease.
- **Systemic staging** of the patient including chest computed tomography, and positron emission tomography. Systemic staging allows an assessment of the extent to which the tumour has spread before or after primary treatment, as this will impact on treatment strategies.
- **Pathological staging** of the mass through examination of tumour tissue by histological, immuno-histochemical, molecular pathological and cytogenetic methods. This information will be important for grading the tumour and providing a histologic diagnosis, which may be relevant to specific treatment strategies and prognosis.

- Biopsy of the tumour is a critical part of planning because it provides tissue for assessing the malignancy or benignity of the tumour, and the histologic diagnosis. The manner by which the biopsy is performed will also have an impact on how subsequent treatment is undertaken. An inappropriately placed biopsy incision, complications of biopsy such as infection and haemorrhage or obtaining unrepresentative tissue may result in amputation, or a lost opportunity for limb sparing surgery. Groups who have the expertise in managing bone and soft tissue sarcomas should perform the biopsy.

2.15.1.2 Principles of limb sparing surgery

As our understanding and management of these patients have improved, the indications for limb salvage surgery have also expanded. When considering the feasibility of limb preservation, the following principles should be taken into account. Firstly, the outcome of surgery with regards to local recurrence, distant metastasis and survival outcome should be comparable to that of ablative surgery. The planned reconstruction should be associated with acceptable risk of complications, possible re-operations and secondary amputation and be reasonably durable. Finally, the functional outcome should be equivalent or better than amputation and should be acceptable to the patient.

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2.15.1.3 Factors that influence the extent of surgery

The extent of surgery is determined by the margins required to achieve local control of disease. Oncologically sound margins are those that give rise to the highest rates of local control of disease. The extent of the margins is multifactorial and include:

- Tumour histology
- Tumour size
- Tumour grade
- Nature of adjacent structures
- Invasion of adjacent structures
- Adjuvant therapies
- Previous surgical manipulation of tumour
- Biopsy
- Fitness of patient
- Potential for limb sparing surgery

Prior to a final decision as to the extent of surgery, full and informed consent must be provided by the patient who may agree with or object to the recommendation of the treating team. Some patients may elect for greater or lesser extents of surgery.

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2.15.1.4 Principles of surgical margins in sarcoma surgery

Surgery with adequate oncologic margins is critical for minimising the risk for local recurrence of disease. Adequate margins are those that remove the tumour in its entirety together with surrounding tissue that may contain microscopic tumour extension or satellites. The manner in which sarcomas grow and, the nature of surrounding tissue abutting the tumour may have a bearing on the planning of surgical margins.

The pseudo-capsule

Most sarcomas have a period of rapid growth. The compression of adjacent tissue produces a pseudo-capsule, which may be visible on anatomic imaging and also at the time of surgery. An inflammatory “reactive” zone caused by the release of tumour related cytokines also surrounds the tumour and includes the pseudo-capsule.[1] This reactive zone is known to contain micro-extensions or satellites of tumour. The pseudo-capsule is unreliable for containing tumour cells and may be mistaken for a more oncologically resilient structure and inadvertently used as a margin for resection.

Surgical margins

Enneking proposed the concept of surgical margins in the management of bone and soft tissue sarcomas. He demonstrated in a retrospective cohort series, that the incidence of local recurrence was 1/45 when the margins were adequate, while in patients where the margins were inadequate, the incidence of local recurrence was 8/8. In that series, he defined adequate margins as following surgery where the entire tumour-bearing compartment was resected.

The modern application of the **Enneking system**[2] describes four types of surgical margins:

Type of margin	Plane of dissection
Intralesional	Passes through the tumour or pseudo capsule.
Marginal	Passes through the reactive zone just beyond the pseudo-capsule
Wide	Passes beyond the inflammatory zone, and includes a cuff of normal tissue around the tumour, which is 2-5 cm thick in the longitudinal axis or includes a named anatomic layer in the radial axis
Radical	Includes the entire tumour-bearing compartment including the origin and insertion of musculo-tendinous structures within the compartment.

The incidence of local recurrence increases as the surgical margin moves closer to the tumour. Radical margins are associated with a local recurrence rate of <5%. Wide margins are associated with a local recurrence rate of 5-15%. Marginal margins are associated with a local recurrence rate of 30-60%. Intralesional margins are associated with a local recurrence rate of 60-100%.

Quality of surgical margins

Following a retrospective cohort study of 503 patients, Kawaguchi et al.[3] proposed a modification of the Enneking system and recommended the following classification:

Type of margin	Plane of dissection
Intralesional	Curettage or debulking
Marginal	Peri-capsular reactive zone
Wide A) Inadequate	Normal cuff of tissue 1cm
Wide B) Adequate	Normal cuff of tissue >1 to <5cm
Curative	Normal cuff of tissue >5cm

In this study, they reported a local control rate of 90% for curative margins, 89% for Wide B margins, 82% for Wide A margins, 60% for marginal margins, and 21% for intralsesional margins. This system was based on the margin distance as measured from the reactive zone.

In designing this classification, they also took into consideration the quality of the surgical margin by the barrier of tissue that was included with the tumour. The authors defined barriers as any tissue, which has resistance to tumour invasion. These included:

- Muscle fascia
- Joint capsule
- Tendon
- Tendon sheath
- Epineurium
- Vascular sheath
- Cartilage
- Pleura
- Peritoneum

The authors sub-classified the barriers into Thick (ITB, presacral fascia, joint capsule) and Thin (muscle fascia, periosteum, vascular sheath, epineurirum) barriers. They then converted the barriers to thicknesses such that:

- Thin barrier = 2 cm of normal tissue
- Thick barrier = 3 cm of normal tissue
- Cartilage = 5 cm of normal tissue
- Adherence of tumour to barrier leads to equivalent reduction of barrier by 1 cm

This approach gives both a quantitative and qualitative measure of the extent of surgery where surgeons may chose to determine the extent of the surgery depending on what tissues are included with the surgical specimen. For example, including the vascular sheath gives a 2cm margin which is associated with an 89% local control rate, suggesting that preserving an important vascular structure may have a local control rate very similar to vascular sacrifice, and therefore, surgeons can chose in such a situation to preserve the vascularity to improve the potential for limb sparing surgery.

Kawaguchi et al.[3] also suggested that the response to neoadjuvant therapy, the grade of the lesion and whether the tumour was a primary or a local recurrence should impact the choice of surgical margin. They advocated wider margins when the response to chemotherapy or radiotherapy was less than a complete response, when radiotherapy was not used, when the lesion was high grade or a recurrence.

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2.15.1.5 Impact of radiotherapy in soft tissue sarcoma on surgical margins

Radiotherapy is an acceptable adjunct to surgery for soft tissue sarcoma whether delivered in pre-operative or post-operative settings.[4][5][6]. Radiotherapy can be delivered via external beam or brachytherapy, or may be given as a continuous course or as a boost after previous radiotherapy. The impact of radiotherapy is on the reduction of local recurrence of disease and in this regard, has been shown to upgrade the quality of surgical margins.[7] Radiotherapy induces a fibrotic rind around the tumour, may reduce the size of the tumour and also reduces the susceptibility of the operative field to seeding if the margins are close.

These effects of radiotherapy can be used to tailor the extent of surgery if limb sparing surgery is contemplated. With the advantages of radiotherapy, the surgical margins may be reduced to leave a more functional limb, or surgery that may avoid the need to resect important neurovascular structures, or musculo-skeletal structures and joints with a similar local control rate of surgery as with wider margins alone.

Low grade tumours are associated with a lower risk of local recurrence. For this reason, some surgeons may choose to operate with closer margins. However, this itself may lead to a higher risk of local recurrence of disease. In a retrospective cohort of cases of low grade soft tissue sarcomas treated by surgery, the addition of radiotherapy was shown to be beneficial when marginal or intralesional margins were employed.[8] Low grade tumours that were smaller than 5cm or excised at a tumour centre with wide margins did not show any additional benefit when radiotherapy was included. The Scandinavian Sarcoma Group also showed that in selected cases of sarcoma a local recurrence rate of 7% was possible with surgery alone.[9]

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2.15.1.6 Impact of chemotherapy in soft tissue sarcoma on surgical margins

Chemotherapy is used selectively in centre-based care for the management of high risk soft tissue sarcoma. A randomised prospective phase III trial of combined chemotherapy radiotherapy for high risk soft tissue sarcoma demonstrated that administration of pre-operative therapies minimised the local risk of relapse and the prognostic impact of close margins on the local and distant outcome.[10] This result may have relevance for patients with high risk soft tissue sarcoma where problematic margins are anticipated.

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2.15.1.7 Impact of inadvertent surgery on soft tissue sarcoma

Between 20-30% of soft tissue sarcomas are treated by inadvertent surgery. The majority of surgeries performed outside a tumour centre are associated with inadequate surgical margins. Banghu et al. reported that 2/3 of patients who underwent surgery outside a specialist centre had positive margins.[11] Goodlad et al.[12] reported that almost 60% of patients who had re-excision of the operative field after inadvertent resection of tumours performed outside a tumour centre had residual tumour tissue. This was despite all patients in their retrospective series being declared widely excised prior to referral. Venkatesan reported that almost ¾ of patients who surgery outside a tumour centre had residual tumour in re-excised specimens.[13] The local recurrence rate of patients treated definitively before referral to a tumour centre is higher than patients who are referred prior to excision.[14]

Patients who have been treated with inadvertent surgery and referred for surgical care require a combination of re-excision and radiotherapy. Patients requiring re-excision of previous operative fields will require much wider surgical margins. If they receive this, published data from retrospective cohort studies demonstrate good local control of disease.[15][16] To achieve local control of disease, re-excision often requires margins that are wider than for the primary tumour.[3]

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2.15.1.8 Impact of response to chemotherapy on osteosarcoma

Chemotherapy induced necrosis is an important factor in determining local recurrence after resection of osteosarcoma.[17] Poor responders were associated with a three times higher risk of local failure. If poor responders also underwent surgery with inadequate margins the risk for local failure rose 50 times. This was in comparison to inadequate surgery in good responders who had a five times higher risk of local failure. These results may be useful for determining the place of amputation in patients known to have sub-optimal response to neo-adjuvant chemotherapy as reflected by restaging studies and in whom the tumour characteristics predicted inadequate margins.

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2.15.1.9 Histology

In principle local recurrence is related to the quality of the surgical margins. However, in certain histotypes, such as low grade chondrosarcomas and well-differentiated lipoma-like liposarcomas, much closer margins than would otherwise be recommended can be employed because the systemic risks of these tumours are low. For example, in grade I chondrosarcomas, some authors advocate thorough curettage of the tumour in combination with chemical adjuvants such as cementation.[18] In well-differentiated lipoma-like liposarcomas marginal excision is recommended if the functional morbidity is unacceptably high because the risk of metastasis is extremely low and recurrence may be treated with re-excision. However, despite the disease free interval not being influenced by resection margin, patients with well-differentiated lipoma-like liposarcoma have a longer disease free interval with the use of adjuvant radiotherapy.[19]

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2.15.1.10 Size and volume

Large size (> 8cm or volume (> 150 ml) of the tumour is generally associated with a poorer prognosis.[20][21] The large size and volume may result in tumours extending outside their original compartments and engaging important neurovascular, musculo-skeletal and joint structures. In addition, larger tumours tend to involve more vital structures that may need to be sacrificed requiring a more extensive reconstruction and poorer functional outcome.

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2.15.1.11 Location

Tumours occurring within the flexor fossae present particular challenges because of the confluence of vital neurovascular structures in these areas and the poor compartmentalization of the tumour which means early and often significant abutment against these important structures. Treatment of tumours in the flexor fossae were traditionally treated with amputation because of the necessity for narrow surgical margins. However with improvements in adjuvant therapy and better medical imaging, these tumours can now be adequately excised with marginal margins and adjuvant radiotherapy or chemotherapy increasing the potential for limb sparing surgery.

In addition, certain tumours such as Ewings,[22] pelvic location greatly influence the overall survival outcome regardless of response to adjuvant therapy and type of surgery. In large pelvic tumours, the role of surgery remains controversial. Reducing tumour burden is thought to be central to effective chemotherapy, however, this must be balanced against the possibility of significant surgical morbidity and functional derangement in the setting of high risk for metastatic disease. Retroperitoneal tumours usually present late and can be quite extensive on presentation. Resectability in these cases depends on response to radiotherapy[23] and the organs involved. Some authors have suggested an aggressive surgical policy. A retrospective case series of 77 patients reported that retroperitoneal sarcoma has a high rate of visceral involvement despite being considered a pushing tumour.[24] This growth pattern may also occur in well-differentiated liposarcoma. That series reported an acceptable five year overall survival of 73%. In palliative situations, incomplete resections may be appropriate to provide symptomatic control and prolong life expectancy.[25]

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2.15.2 Evidence summary and recommendations

Importance of surgical margins

Evidence summary	Level	References
The risk of local recurrence is related to the surgical margins achieved.	II, III-3, IV	[3], [26], [27], [28], [29], [4], [17], [19], [20], [22], [30]

Evidence-based recommendation	Grade
It is important that wide surgical margin is achieved to prevent local recurrence and poor survival outcomes.	**B**

Unplanned excision

Evidence summary	Level	References
Unplanned resection of musculoskeletal tumours often result in positive margin surgery. This is associated with higher risk of local recurrence, distant metastasis and poorer survival outcomes. Re-resection often require wider margins and may lead to poorer functional outcome.	III-3, IV	[31], [13], [12], [32], [14], [16], [33]

Evidence-based recommendation	Grade
Musculoskeletal tumours are best managed in a specialist sarcoma unit by a multidisciplinary team.	**C**

Evidence-based recommendation	Grade
Soft tissue sarcomas initially excised with residual disease and/or positive margins will require re-excision, preferably in a specialist sarcoma unit. These tumours should be re-excised with wide margins and usually require adjuvant radiotherapy.	**C**

Retroperitoneal sarcoma

Evidence summary	Level	References
Retroperitoneal sarcomas can be extensive and involve multiple organs. Good results can be achieved, but require an aggressive approach. When carried out in a specialised tumour centre, surgery is safe and is associated with improved local control.	III-3, IV	[34], [35], [36], [37], [38], [24]

Evidence-based recommendation	Grade
Retroperitoneal sarcomas are best managed in a specialised tumour centre by a multidisciplinary unit.	**C**

Limb salvage surgery in Osteosarcoma

Evidence summary	Level	References
Limb salvage surgery has higher rates of survival and lower secondary amputation. There is no survival advantage from amputation.	III-3	[39], [40]

Evidence-based recommendation	Grade
Limb salvage surgery is an acceptable treatment in the management of osteosarcoma.	**C**

Effective radiotherapy on limb salvage

Evidence summary	Level	References
Epineural dissection in conjunction with pre-operative radiotherapy is a safe and effective technique to preserve vital nerves.	III-2	[41]

Evidence-based recommendation	Grade
Pre-operative radiation therapy may allow preservation of vital structures without compromising local control.	**C**

Evidence summary	Level	References
Radiotherapy is an important adjunct to the management of soft tissue sarcoma (STS) and reduces the risk of local recurrence.	II, III-2, IV	[42], [23], [43], [44], [4], [6], [10]

Evidence-based recommendation	Grade
Pre or post-operative radiation therapy should be considered in the management of soft tissue sarcoma. Decision should be made in the setting of a multidisciplinary team.	**A**

Isolated limb perfusion

Evidence summary	Level	References
Isolated limb perfusion can be effective in facilitating limb preservation surgery.	III-3, IV	[45], [46], [47], [48]

Evidence-based recommendation	Grade
Isolated limb perfusion should be considered in patients with extensive soft tissue sarcoma where there is doubt whether limb salvage surgery can be achieved. Decision should be made in the setting of a multidisciplinary team.	C

Chondrosarcoma

Evidence summary	Level	References
Grade 1 chondrosarcoma the distinction of which can be difficult from endchondroma both on imaging and pathology grounds can be safely managed with close follow-up and a multidisciplinary diagnosis. Grade 1 chondrosarcoma can be treated with intralesional excision safely.	III-3, IV	[49], [18], [50]

Evidence-based recommendation	Grade
Grade 1 Chondrosarcoma can be safely managed with intralesional excision with cementation. Distinction between this and other grades requires correlation of clinical and radiological features.	C

Practice point
Any lump greater than 5 cm or deep to the deep fascia should be considered a sarcoma until proven otherwise.

Practice point

Persistent and unremitting pain, not responsive to oral analgesics and nocturnal in occurrence should stimulate investigation for a bone tumour.

Practice point

Complete imaging (anatomic and functional including XR, CT, MRI, nuclear scan) should be undertaken of a bone and soft tissue tumour prior to surgical manipulation.

Practice point

Biopsy should be performed under image guidance to determine the track of the biopsy, and the target of the biopsy to confirm representativeness. Computed tomographic guidance is recommended. Biopsy should be performed after all imaging modalities have been completed to minimise the impact of biopsy induced image artifact.

Practice point

Sarcomas are best managed at a specialist sarcoma unit.

Practice point

Local recurrence is related to the adequacy of surgical margins. Wide surgical margins should be employed for bone and soft tissue sarcomas except when close margins are planned and adjuvant radiotherapy /chemotherapy is employed.

Practice point

Tissues of different resistance to tumour invasion that surround a tumour may be used to calculate the quality of surgical margins. In this way, more careful planning of surgical margins may be undertaken when contemplating limb-sparing surgery.

Practice point

Combination therapy is required to adequately manage bone and soft tissue sarcomas. Radiotherapy and wide margin surgery are used for soft tissue sarcomas. Chemotherapy and wide margin surgery are used for bone sarcomas.

Practice point

Radiotherapy is recommended for low grade soft tissue sarcomas particularly if these tumours are large and excised with marginal margins.

Practice point

Adequacy of surgical margins achieved should be assessed by a expert musculoskeletal pathologist. Refer to the Royal College of Pathologists of Australasia Soft Tumour Resection Structured Reporting Protocol 1st Edition 2011

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2.15.4 Appendices

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2.16 Reconstructive options

Contents

2.16.1 What are the factors that impact on the choice of reconstructive options in BSTTs?

2.16.1.1 Introduction

Reconstructive surgery in the management of sarcoma is a broad and varied field and the reconstructive surgeon is an integral member of the multidisciplinary team.

The first priority is oncological resection of sarcoma with sufficient margins. Reconstruction aims to return optimal function and appearance to the affected area. When this involves the limb, the preference is for reconstruction (termed limb salvage surgery) though occasionally removal of part or all of the limb may be required (termed limb ablative surgery).

During oncological resection, preservation of functionally critical neurovascular structures is desired (e.g. common femoral artery, sciatic nerve in lower limb). Where preservation of critical structures is not possible, consideration is given to reconstruction of these elements (e.g. reconstructing arterial conduit). Where reconstruction is not possible, this may necessitate a limb ablative surgical approach (e.g. amputation).

When it is possible to preserve or reconstruct critical neurovascular structures, reconstruction focuses on:

1. Bone
2. Soft tissue covering
3. Functional transfer for absent muscles, nerves

Bony reconstruction can be:

- No formal reconstruction
- Alloplastic reconstruction
- Non-vascularised autologous reconstruction
- Vascularised autologous reconstruction
- Extracorporeal irradiated autologous reconstruction
- Cadaveric bone reconstruction

Bony resection has added considerations of proximity to critical skeletal elements - especially joints and joint stabilising structures, as well as the physis (growth plate) in the skeletally immature. Involvement of these structures necessitates more major excision and thus reconstruction.

When dealing with younger individuals skeletal growth is an added consideration, but secondary to safe oncological clearance. Due to the adaptability of the paediatric population however often more novel surgical procedures can be undertaken with the hope of true biological reconstruction. On occasion prosthetic reconstruction must be used however, and technology in this field is also advancing (e.g. "growing" prostheses, custom made prostheses), outcomes differ for different skeletal sites.

Soft tissue reconstruction incorporates replacement of:

- Skin/soft tissue cover
- Important neurovascular structures
- Muscle if critical for function

Factors affecting choice of soft tissue reconstruction:

- Patient factors
  - -General health (age, body mass index (BMI), functional status, nutritional status)
  - -Smoking
  - -Diabetes
  - -Cardiovascular disease
  - -Neurological disease
- Tumour pathology features
- Resection wound features
  - -Location
  - -Bony reconstruction requirement
  - -Exposed bone/tendon/alloplastic reconstruction
- Treatment related factors
  - -Peri-operative chemotherapy
  - -Peri-operative radiotherapy

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2.16.1.2 General principles of reconstruction in sarcoma

General principles in keeping with management of reconstruction in all patients:

- Patient general optimisation
  - -Nutrition
  - -Minimise smoking
  - -Diabetic control
  - -General complication reduction (measures including DVT prophylaxis, chest physiotherapy, peri-operative antibiotics)
- Optimal resectional surgery (tumour clearance, minimal injury to critical reserved structures)
- Optimal bony reconstruction, where required

Effect of general factors on reconstructive options

There is a significant benefit to patient outcome with extremity soft tissue sarcoma if the patient is better educated, optimistic, with better baseline health-related quality of life. [1]

Management of lower limb sarcoma cases following unplanned (Whoops) primary procedure is more complex with greater resectional surgery and more complex reconstructive surgery required, often with vascularised tissue.[2]

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2.16.1.3 Specific principles of soft tissue reconstruction in sarcoma

Choice of reconstructive techniques

Due to the size and complexity of resectional defects for sarcomas, soft tissue coverage with vascularised soft tissue flaps should be considered in all cases, both in children and adults. This is supported by several studies showing improved functional outcome and lower wound complications when vascularised soft tissue coverage procedures, such as myocutaneous and fasciocutaneous flaps are used.[3] [4] [5]

Effects of radiotherapy on reconstructive options

Radiotherapy to area (in any form) reduces vascularity and impairs wound healing. Radiotherapy (particularly pre-operative radiotherapy) leads to a higher rate of complications (OR 2.67) than those not treated with radiotherapy, in extremity soft tissue sarcoma.[3]

In the only randomised controlled study comparing complications of pre-operative and post-operative radiotherapy, pre-operative therapy was shown to reduce radiotherapy-related morbidity and increase surgical morbidity. [6] A well-designed retrospective case series review also confirmed these findings. [3] Another retrospective study with substantial biases and confounders, comparing post-operative and pre-operative radiotherapy in development of complications, suggested post-operative radiotherapy may lead to a higher rate of complications than pre-operative radiotherapy. (This last study was retrospective, with no case-control matching for factors affecting healing, tumour location and previous surgical intervention, and quite disparate groups when these factors were reviewed.) [7]

Vascularised soft tissue coverage (often with greater surgical complexity) is recommended in cases treated with pre-operative radiotherapy to reduce the risk of wound complications. [6] When pre-operative radiotherapy is used in treatment of sarcoma, vascularised tissue coverage has a lower complication profile in reconstruction of surgical defect compared to direct closure. [8] When wound complications occur after pre-operative radiotherapy and resection of extremity soft tissue sarcoma, vascularised soft tissue coverage is an effective management tool. [9]

Vascularised soft tissue coverage following resection of extremity soft tissue sarcomas tolerates post-operative radiotherapy with low wound complication rate (5%). [10]

Effects of chemotherapy on reconstructive options

Cytotoxic chemotherapy impairs wound healing. Timing of chemotherapy should be coordinated with planning of resectional and reconstructive surgery to minimise wound healing problems and infection risk (especially in the setting of major resections with prosthetic/allograft reconstruction).

Additional considerations in vascular reconstruction

When resection of extremity soft tissue sarcoma requires removal of major vascular supply to the limb, reconstruction of either the artery alone, or the artery and accompanying vein, have equivalent results. [11]

Additional considerations in nerve and muscle reconstruction

When significant nerve resection is required, consideration should be made for reconstruction of this with vascularised or non-vascularised nerve graft.

When substantial functional deficit results from muscle resection, consideration should be made to transpose other muscles to provide this function, or use free tissue transfer of vascularised, neurotised muscle to provide the absent function.

Reconstruction in specific sites

Head and Neck

- Undertake careful planning in this functionally and aesthetically sensitive area to:
  - Reconstruct bony framework and contour, restore functional elements (as relevant, ocular cover if eye preserved, oral competence, facial nerve reconstruction, functional muscle reconstruction), soft tissue /skin cover.

Lower extremity

- Due to the limited bulk of soft tissue and diminished laxity in the lower leg, soft tissue coverage of sarcoma defects in this area often requires free tissue transfer to provide vascularised soft tissue coverage. These techniques are safe and effective in this patient group. [12]
- Pedicled gastrocnemius flap is an useful technique to cover soft tissue defects of the knee and is clinically reliable and effective. [13] It is also a useful adjunct to extensor mechanism repair where either proximal tibial or patella tendon excision has been required.

Upper extremity

- Due to limited soft tissue laxity in the upper limb area, particularly the forearm and hand, often free tissue transfer or regional flaps are required to provide vascularised soft tissue coverage for sarcoma defects. Free flaps are more often required in distal defects (e.g. hand, wrist), while pedicled flaps are used more often in proximal defects (e.g. shoulder) due to greater available options. These techniques are reliable and effective in the reconstruction of both bony and soft tissue defects. Pedicled and free flap reconstruction have equivalent good functional outcomes when required in upper limb sarcoma reconstruction[14] [15] [16] [17] **add ref Payne
- Sarcomas of the forearm and hand are best managed by a specialist team to enable optimal reconstruction and functional outcome. [18]
- Pedicled latissimus dorsi flap is an useful technique to cover soft tissue defects of the shoulder and is clinically reliable and effective. [19]

Chest wall

- Reconstruct chest wall in layers. Polypropylene mesh with vascularised flap coverage has shown to be a functionally acceptable option in reconstruction of this area.[20][21] Thoracoplastic techniques to utilise locoregional muscle flaps in reconstruction should also be considered preoperatively. [21]

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2.16.1.4 Specific principles of bony reconstruction in sarcoma

Reconstruction in areas of the bone which are not in close proximity to joints (metadiaphyseal, diaphyseal location) is necessary to return structure and function to the limb. Bone reconstruction near to joints or with epiphyseal involvement is generally more complex. Available options vary relating to the location – in some areas, prosthetic joint replacement is a stable option with acceptable function and longevity, whereas in other locations options such as fusion may be preferred.

Function is the priority in bony reconstruction. This can be assessed by a number of measures. These measures focus on both location specific function (such as range of movement, stability, and level of discomfort) and also functional status in general activities (both psychological and physical). Tunn recommends that multiple measures of function and outcome are adviseable (eg MSTS, TESS, RNL, ISoLS). [22]

It is generally accepted that, where possible, limb salvage procedures result in better functional outcomes, but do not necessarily result in greater quality of life. [23] [24] [25] [26] [27] [28] [29][30] [31] Robert examined long term outcomes of patients following limb salvage and limb ablation, and found that patients undergoing late amputation (due to failed limb salvage) fare worse psychologically due to greater difficulty with body image.[32]

Reconstruction in metadiaphyseal areas

- A number of options are available with preference for a biological reconstruction where possible.
- Examples of autologous vascularised bone incude the vascularised fibula flap. This is a reliable and functionally effective technique to reconstruct bony defects following sarcoma resection. [33]
- Bone that has undergone extracorporeal irradiation has also been successfully used. [34] [35]
- as has prosthetic (metallic) intercalary reconstruction.
- Sometimes combinations of the above are used.[36][37][38][39][40]

Periarticular reconstruction

EndoProsthetic reconstruction has been shown to have acceptable oncological and functional results[41][42][43] [44][45] [46][47][48][49][39][50] in setting of pathological fracture. [51] [52] [25]

Muscolo has shown acceptable outcomes with osteoarticular allograft, though Kim showed poor outcomes with osteoarticular autograft that had undergone extracorporeal irradiation.

The varied results and techniques available reflect differing experience and technical availability at different centres, but it is accepted that this highly specialised surgery is performed at centres with particular expertise in sarcoma surgery.

Reconstruction in specific joint locations

Reconstruction of specific joint areas should be tailored to the needs of the individual patient. Priority is given to ensure maintenance of neurovascular structures crossing joints to provide distal function, and muscle groups acting on the joint are also preserved or reconstructed. Preferred options for managing specific joint locations follows:

Upper limb:

- Hand – distal amputation with no, or delayed reconstruction in digits. Resection of affected area and reconstruction with bony support in proximal hand.
- Wrist – fusion is preferred management at this site.
- Elbow - use of prosthesis.
- Shoulder – use of prosthesis or resection (arthrectomy).

Lower limb:

- Foot - amputations tailored to specific site.
- Ankle fusion is preferred management at this site.
- Knee - use of prosthesis.
- Hip - use of prosthesis.

Pelvis:

- Many reconstructive options are available in the pelvis due to the complexity of the anatomy and size. In general principles, survival outcomes are improved with wide/radical resection in this area but complication rates of reconstruction are often high.

Spine:

- Unique anatomy again determines resectability whilst maintaining spinal cord function, but where possible total or subtotal vertebrectomy can be performed with various stabilisation options, including combination cage and plating anteriorly with instrumented pedicle fixation posteriorly.

Reconstruction in the growing skeleton

To allow optimal growth in children, consideration should be made to use a growing prosthesis (in the setting where physeal resection is required).[53][54][43][55][43]

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2.16.2 Evidence summary and recommendations

Evidence summary	Level	References
Improved patient outcome with extremity soft tissue sarcoma if patient is better	III-3	[1]

Evidence summary	Level	References
educated and optimistic.		

Evidence-based recommendation	Grade
Provision of education and psychological support is an important component in holistic care of the sarcoma patient.	**C**

Evidence summary	Level	References
Unplanned primary surgery in the management of lower limb sarcomas requires more complex resection and reconstruction, often with vascularised tissue.	IV	[2]

Evidence-based recommendation	Grade
Sarcomas are better managed in a specialist sarcoma unit with planning of primary resection, reconstruction and timing of radiotherapy (where required) for optimal outcome.	**D**

Surgical reconstruction options

Evidence summary	Level	References
Vascularised tissue coverage is safe and effective in management of extremity soft tissue sarcomas requiring larger resections and post-operative radiotherapy.	III-2	[3]
Vascularised tissue coverage with myocutaneous and fasciocutaneous flaps in extremity soft tissue sarcoma reconstruction is reliable and assists in limb preservation.	IV	[4]
Vascularised soft tissue coverage is safe and effective in the management of sarcomas in childhood.	IV	[5]

Evidence-based recommendation	Grade
Consider vascularised tissue coverage in management of soft tissue sarcomas, particularly when large resections or radiotherapy expected, and in children.	**C**

Radiotherapy effects

Evidence summary	Level	References
Radiotherapy (particularly pre-operative radiotherapy) leads to a higher rate of complications than those not treated with radiotherapy (OR 2.67) in extremity soft tissue sarcomas.	III-2	[3]
Pre-operative radiotherapy leads to a higher wound complication rate in comparison to post-operative radiotherapy.	II	[6]
Post-operative radiotherapy may lead to a greater radiation-related complication profile in comparison to pre-operative radiotherapy in treatment of sarcoma.	III-2	[7]

Evidence-based recommendation	Grade
Recognise that pre-operative radiotherapy leads to a higher wound complication profile than (i) no radiotherapy, and (ii) post-operative radiotherapy.	**B**

Evidence summary	Level	References
Reconstruction of sarcoma defects treated with pre-operative radiotherapy is more effective when vascularised flap closure is used, particularly free tissue transfer.	III-2	[8]
Pre-operative radiotherapy leads to a greater use of vascularised flap coverage of soft tissue sarcoma defects.	II	[6]
Following pre-operative radiotherapy, reconstructive surgery with vascularised soft tissue coverage is often indicated to manage later wound complications in extremity soft tissue sarcoma.	IV	[9]

Evidence-based recommendation	Grade
Consider vascularised flap coverage (including free tissue transfer) in reconstruction of sarcoma defects following pre-operative radiotherapy.	**B**

Evidence summary	Level	References
Vascularised soft tissue coverage after resection of extremity soft tissue sarcomas is resilient when treated with post-operative radiotherapy, with low wound complication rate.	IV	[10]

Evidence-based recommendation	Grade
Consider vascularised flap coverage (including free tissue transfer) in reconstruction of sarcoma defects when post-operative radiotherapy is anticipated.	**D**

Reconstruction of vascular defects

Evidence summary	Level	References
When vascular resection is required in management of extremity sarcoma, reconstruction of artery alone, or artery and vein, have equivalent outcome.	IV	[11]

Evidence-based recommendation	Grade
When restoration of vascularity to a limb is required following sarcoma resection, prioritise arterial reconstruction and consider the need for venous reconstruction.	**D**

Lower extremity

Evidence summary	Level	References
Free tissue transfer in reconstruction of lower limb soft tissue sarcoma defects is safe and effective.	IV	[12]

Evidence-based recommendation	Grade
Consider vascularised tissue in reconstruction of bone and soft tissue in lower extremity sarcoma.	**D**

Upper extremity

Evidence summary	Level	References
Vascularised soft tissue coverage of soft tissue sarcoma defects in upper limb is reliable and effective, particularly in management of large tumours, recurrent disease and following pre-operative radiotherapy..	IV	[14], [15], [16]
Vascularised fibular flap is a reliable and effective tool in reconstruction of bony sarcoma defects in the upper limb.	IV	[17]

Evidence-based recommendation	Grade
Consider vascularised tissue in reconstruction of bone and soft tissue in upper extremity sarcoma.	**D**

Forearm and hand

Evidence summary	Level	References
Reconstruction of sarcomas in forearm and hand is challenging and is best managed by a specialist team for best functional outcome.	IV	[18]

Evidence-based recommendation	Grade
Referral to specialist hand and upper limb surgical team to be sought when surgical resection and reconstruction is required for sarcoma in the hand and forearm area.	**D**

Chest wall

Evidence summary	Level	References
Reconstruction of chest wall sarcoma defects with mesh and vascularised regional flaps, including pectoralis major and latissimus dorsi muscles, are safe and effective.	III-2	[20], [21]

Evidence-based recommendation	Grade
Consider incorporation of thoracoplastic techniques with mesh and vascularised flap coverage in management of chest wall defects following sarcoma resection.	**C**

Bony reconstruction

Evidence summary	Level	References
Reconstruction of skeletal elements is age, site, and tumour specific and requires specific knowledge and experience of surgical and adjuvant therapies, as there are wide ranging options available.	IV	[33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54]

Evidence-based recommendation	Grade
The decisions for reconstruction of skeletal elements are ideally made at a specialist sarcoma unit.	**D**

Practice point

The nature of reconstruction of defects following sarcoma resection is often complex due to the required size of resection, likelihood of need for perioperative radiotherapy with associated surgical challenges, and variation in involved tissue types. Specialist Multidisciplinary Team management is advised for all cases for optimal outcome.

Practice point

Optimisation of general patient factors, both physical (including diabetic control, nutrition, minimising smoking and avoiding preventable perioperative morbidity) and psychological, will provide benefits to patient outcome. Patient education regarding the disease process and treatment options is also important in achieving the best holistic outcome.

Practice point

Radiotherapy (in any form) reduces vascularity and impairs wound healing. Reconstructive options are affected by choice and timing of radiotherapy. A treatment plan for each case should be discussed at commencement of treatment to determine best timing and choice of surgical resection, surgical reconstruction and radiotherapy. This will allow best outcome with minimisation of surgical-related and radiotherapy-related morbidity.

Practice point

When limb-preserving surgery is undertaken, care should be taken to reconstruct all resected tissues. This includes skeletal stability in bony reconstruction, reconstruction of neurovascular structures and functional muscle groups, and overlying soft tissue coverage.

Practice point

In all resection defects requiring soft tissue coverage, vascularised tissue is the preferred reconstruction. This may be in the form of locoregional flap transfer, or free flap tissue transfer with reconstruction of the tissue vascularity using micro-surgical anastamoses of blood vessels. This enables best healing of underlying structures, reduces infection and other complication risks relating to skeletal implants, and provides greatest resilience to radiotherapy.

Practice point

Restoration of function is the priority in reconstruction of the bony skeleton. Many options are available for reconstruction in metadiaphyseal areas, with preference for biological reconstruction where possible. Endoprosthetic reconstruction is commonly used in periarticular reconstruction.

Practice point

Limb salvage procedures result in better functional outcomes, but do not necessarily result in greater quality of life.

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2.16.3 Issues requiring more clinical research study

- Assessment of value of combined specialist multidisciplinary clinics in management of sarcomas.
- Multi-centre trials assessing specific reconstructions of anatomical locations.
- Multi-centre trials assessing timing of radiotherapy, relationship to reconstruction and long term function and quality of life outcomes.

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2.17 Preoperative optimisation strategies

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2.17.1 What pre-operative optimisation strategies improve outcomes in BSTTs?

2.17.1.1 Introduction

A number of pre-operative optimisation strategies have been proposed to improve outcomes in patients undergoing complex cancer resection. Most of these studies involve multi-modality interventions, such as ‘fast track protocols’ to optimise nutritional, analgesia and mobility outcomes and reduce surgical morbidity and/or transfusion requirements.

Other preoperative strategies, such as preoperative embolisation are aimed at reduction of intraoperative blood loss.

There is limited evidence to support the use of targeted pre-operative therapies.

2.17.1.2 Pre-operative embolisation of bone neoplasms

A limited number of publications describe the use of gelatin microspheres or polyvinyl alcohol particles as pre-operative embolisation strategy for bone neoplasms.[1][2] Whilst well described for palliation of unresectable bone tumours or giant cell tumours of the sacrum, there is limited data to support the use of embolisation pre-operatively for sarcoma. No randomised controlled trials (RCTs) have been conducted comparing the use of embolisation with either no-preoperative intervention or with an alternate modality.

2.17.1.3 Pre-operative embolisation in retroperitoneal sarcoma

Pre-operative embolisation is sometimes considered prior to resection of large intra-abdominal tumours. The rationale of this approach is to reduce operative blood loss, and facilitate surgical resection. Whilst some data suggests that this approach is safe,[1][2] no RCTs have been conducted to compare the use of embolisation with either no preoperative intervention or with an alternate modality.

2.17.1.4 Pre-operative imatinib mesylate in dermatofibrosarcoma

Kerob et al conducted a Phase II multicentre study of 25 patients and report a benefit for patients with dermatofibrosarcoma treated with imatinib mesylate.[3] This data, whilst limited, support the consideration of imatinib in the pre-operative setting in non-resectable DFSP or when surgery is difficult or mutilating.

2.17.2 Evidence summary and recommendations

Evidence summary	Level	References
Use of pre-operative embolisation in selected cases may decrease operative blood loss and facilitate surgical resectability.	IV	[1], [2]

Evidence-based recommendation	Grade
Pre-operative embolisation may be considered in selected cases.	**D**

Evidence summary	Level	References
Pre-operative Imatinib mesylate may benefit selected patients with DFSP.	IV	[3]

Evidence-based recommendation	Grade
Pre-operative imatinib mesylate may be considered in selected patients with DFSP when surgery is difficult or potentially mutilating.	**D**

Practice point
It is advisable to consider the suitability and applicability of pre-operative optimisation strategies, such as embolisation, prior to surgery for large or complex BSSTs.

2.17.3 Issues requiring more clinical research study

A number of gaps in the evidence have been identified. These include:

- What is the role of preoperative embolisation?
- What is the role for 'fast track' protocols in management of BSSTs?

2.17.4 References

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2.18 Regional chemotherapy

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2.18.1 What is the role of regional chemotherapy in BSTTs?

2.18.1.1 Introduction

The major goal of treating sarcoma in the extremities is to achieve long-term control and to preserve function wherever possible. This is particularly important as amputation does not improve survival rates in patients with large (>5cm) deep-seated high grade sarcomas. Limb salvage offers significant benefit to the patient and community in terms of function, work productivity, rehabilitation and overall cost.

Surgical therapy remains problematic for patients with large primary tumours and those with bulky recurrent disease. Local recurrence rates are directly related to the type and extent of surgery and/or radiotherapy undertaken and range between 10-80%. Criteria of irresectability include multifocal primary tumours, multiply recurrent limb tumours, fixation to or invasion into neurovascular bundles and/or bone and tumour recurrences in previously irradiated areas.

Isolated limb perfusion (ILP) has been used in patients with extremity STS for > 40 years. In the majority of patients, this approach has been used as a limb-sparing alternative when amputation was considered the only treatment option.

The proposed advantages of ILP include: isolation from the systemic circulation which permits administration of high dose cytotoxic chemotherapy; tumouricial effects of hyperthermia and potentially down-staging of STS which may permit subsequent limb sparing surgery.

Several contentious questions persist in relation to the appropriate drug or drug combinations, the use of tumour necrosis factor – alfa (TNFα), the use of ILP in the pre-operative setting and the use of isolated limb infusion (ILI) as an alternative to isolated limb perfusion (ILP).[1]

Several large studies from European centres suggest that ILP with combination melphalan and TNFα should be considered as first line therapy for patients with large high grade primary extremity STS. However, it is not possible to subject this treatment to a true randomised control trial as STS is a relatively rare condition.[2]

Australian experience with ILP is limited to only a few specialised centres. TNFα is not currently available in Australia due to licencing issues.

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2.18.1.2 Role of ILP in limb salvage, prior to consideration of amputation

No randomised controlled trial or other comparative study was available comparing ILP with other treatment options (e.g. pre-operative or amputation) for locally unresectable soft tissue sarcoma (STS).

The best available evidence (i.e. largest series) comes from a retrospective, multicentre study involving eight European centres,[3] each of which used a standardised protocol with melphalan and TNFα in 186 patients.

Clinical complete response was observed in 33 patients (18%), partial in 106 patients (57%), stable disease in 42 (22%) and tumour progression in five patients (3%). In 126 patients (68%) the tumour remnant was surgically excised after ILP. In patients undergoing post ILP resection, histopathological responses were: complete response 29%, partial 53%, no change 16%, tumour progression 2%. The limb salvage rate was 82%. Regional toxicity was found to be moderate in most (171 patients). One patient developed grade V toxicity and required amputation. Systemic toxicity was moderate and no therapeutic interventions were required.

These findings are consistent with other series from different institutions, reporting overall response rates for ILP in unresectable STS varying between 77% to 94%, with acceptable regional and systemic toxicity.[4][5]

ILP is also warranted for patients with metastatic disease, and advanced local extremity disease, as an alternative to amputation.[6]

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2.18.1.3 Efficacy of ILP with melphalan alone vs melphalan + TNFα

ILP is provided in a limited number of Australian centres. Some centres provide a simplified version of ILP called isolated limb infusion (ILI). ILI utilises a low-pressure hypoxic circuit rather than an oxygenated pressurised perfusion circuit. One Australian study reports a series of 21 patients with extremity STS undergoing ILI. The overall response rate was 90% and the overall limb salvage rate 76%.[7] Systemic leakage monitoring is not performed with ILI, making it unsuitable for use with TNFα.

Melphalan is the standard cytotoxic aged used in ILP. Other cytotoxic agents such as cisplatin and doxorubicin have been used and report similar efficacy. More recently TNFα has been used in combination with melphalan to increase efficacy rates. TNFα has indirect antitumour effects on the tumour vascular bed.[1] Although most single centre series report higher response rates with melphalan + TNFα for extremity sarcoma, there are no randomised studies comparing with melphalan. The toxicity profile of TNFα mandates systemic leakage monitoring. TNFα is not available in Australia for ILP.

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2.18.2 Evidence summary and recommendations

Evidence summary	Level	References
Isolated limb perfusion is an effective limb-sparing option for patients with unresectable extremity soft tissue sarcoma. In selected patients it may provide an alternative to amputation; as either a 'downstaging' strategy for otherwise unresectable disease, or as a palliative strategy.	IV	[4], [5], [3], [1]
The efficacy of isolated limb perfusion (ILP) with melphalan is increased when combined with TNFα*.	IV	[1]

* TNFα is not licenced in Australia.

Evidence-based recommendation	Grade
Isolated limb perfusion (ILP) may be considered as a palliative alternative to amputation in patients with extremity soft tissue sarcoma.	**D**

Practice point
The toxicity of isolated limb perfusion (ILP) with melphalan is increased when combined with TNFα.

Practice point

ILP may be considered to downstage extremity soft tissue sarcoma when primary amputation would otherwise be considered.

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2.18.3 Issues requiring more clinical research study

A number of gaps in the evidence have been identified. These include:

- What is the ideal cytotoxic drug (or combination) for isolated limb perfusion (ILP)?
- What is the role of ILP in the neo-adjuvant setting?

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2.19 Treatment responses assessment

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2.19.1 What are the measures to assess treatment response in BSSTs?

2.19.1.1 Introduction

For some sarcomas of the bone, particularly osteosarcoma and the primitive neuroectodermal tumours (PNET) /Ewing's family of tumours, histologic evidence of a substantial level of treatment induced tumour necrosis has been found to be predictive of improved long term survival and conversely patients with a poor response are at an increased risk for local recurrence.[1][2][3][4][5] Patients in whom treatment induces necrosis in at least 90% of their tumour have superior survival compared to those with lesser levels of response.[6] Data are more conflicting regarding the prognostic significance of necrosis in other soft tissue sarcomas.[7][8][9][10][11] This is related in part to the greater heterogeneity of soft tissue subtypes and to the inherent necrosis associated with high grade sarcomas unrelated to therapy effect.

2.19.1.2 Pathologic assessment of post therapy tumour necrosis

Post chemotherapy tumour necrosis is a powerful predictor of survival in patients with skeletal osteosarcoma and Ewing's tumour. To assess pathologic response, one complete thin slice of tumour is taken through its largest axis. This is decalcified promptly. The entire specimen is sequentially embedded into blocks and the location of the blocks is mapped. Tumour necrosis is evidenced by sclerosis of bone and cell drop out, granulation tissue or coagulative tumour necrosis. The percentage of tumour necrosis is estimated in a semi-quantitative mmanner.[12][3][13]

The response is graded based on percentage of necrosis as follows:

% Necrosis	Grade of Pathologic Response
≤50%	I
50-≤90%	II
90-99%	III
100%	IV

Tumours with at 95% or more necrosis have a superior prognosis.

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2.19.1.3 Pre-operative therapy and prediction of response

Given the large size of many bone and soft tissue sarcoma (STS), the possibility of achieving tumour shrinkage prior to surgical resection has appeal. If effective, this intervention may make more patients eligible for limb sparing surgery and indeed may make surgery a possibility, particularly for surgically challenging sites. Both

combination chemotherapy and radiation therapy have been used in the pre-operative setting. Courses of such pre-operative therapy are administered over a number of weeks to months in the lead up to the planned resection. In this context, there is a risk that the tumour will not respond to the pre-operative therapy and may even grow or spread in the interim, the delay potentially rendering the tumour unresectable. Monitoring of the patient and tumour during the pre-operative phase is required to assess the response to pre-operative therapy and to tailor the approach, in case of a suboptimal response.

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2.19.1.4 What approaches are used to monitor response to pre-operative therapy?

Two principal approaches have been used to monitor pre-operative response. One involves gauging significant changes in tumour size, through static imaging techniques, such as plain X-rays, computed tomography (CT) scans and Magnetic Resonance Imaging (MRI).

The other approach focuses on functional changes in the neoplasm induced by treatment. Monitoring changes in blood flow by angiography and colour Doppler sonography or recording the alterations in glucose metabolism by positron emission technology are examples of this approach.

In both settings, changes in specific parameters of interest are recorded by comparing pre-treatment data to repeat measurement carried out at predefined intervals during the treatment phase. After resection, these pre-operative changes are correlated with the degree of tumour necrosis as assessed by histopathological examination.

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2.19.1.5 How predictive are the various response monitoring systems of histopathological tumour necrosis?

CT scans and MRI have been used for evaluating changes in size. Conventional radiography cannot adequately depict the soft tissue component of sarcomas and is not reliable for assessment of response.[14] Techniques that assess changes in size are of most value in the setting of tumour progression. Even in the setting of substantial tumour necrosis, sarcomas may not shrink significantly, at least in the short term. Furthermore, cystic change and oedema induced by the therapy may even cause enlargement. In STS, while tumour growth was highly predictive of a poor response, stability or reduction in size predicts had only a 50% chance of being associated with a good response.[15][16] Similarly, in osteosarcomas increased signal intensity on MRI predicted poor response but the reverse did not hold for good response. In the setting of pre-operative radiation therapy for STS radiologic size increase was not predictive of poor response.[17]

For the purposes of documenting changes in size, the Response Evaluation Criteria In Solid Tumors (RECIST) criteria are preferred over the more complex World Health Organisation (WHO) criteria.[18] There is some evidence that the adapted Choi criteria, using a combination of reduced tumour size and decreased density on contrast-enhanced CT, are more predictive of response in soft tissue sarcomas, particularly for Gastrointestinal Stromal Tumours (GISTS).[19]

Functional imaging has focused on fluorodeoxyglucose positron emission tomography (FDG PET) imaging, often in combination with volumetric approaches (CT or MRI). Positron emission tomography (PET) standard uptake value (SUV) has been suggested to be proportional to the proliferative rate of the neoplastic cells. Changes in the SUV have been found to correlate with percentage necrosis both in osteosarcoma and the Ewing family of tumours.[20][21] However the specific SUV indices used and the timing of the PET scan after the start of therapy are widely variable.

For osteosarcomas of the extremities, the Metabolic Tumor Volume (MTV), defined as the volume of tumor tissue with an SUV above a minimum threshold of 2.0 by 18F-FDG PET/CT was found recently to correlate with both pathologic response and survival.[22] There was also some evidence of gradation of outcome by pathology response and MTV. PET has the added advantage that a metabolic response precedes volumetric response by several weeks, such that in osteosarcomas useful changes were documented even after the first cycle of chemotherapy.[23] Furthermore, PET provides whole body imaging, useful for detecting occult metastases in the lungs, bones and viscera.

Scintigraphy using 99mTc-MIBI,[24] or 201Tl[25] imaging has also been used to predict response to chemotherapy in bone and soft tissue sarcomas. Changes in specific indices of these radioisotopes have been found to correlate with percentage necrosis. Doppler ultrasound has been used to gauge changes in blood flow through the sarcomas as a result of therapy and an increase in arterial resistance was found to correlate with histologic response in osteosarcomas.[26][27]

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2.19.1.6 Other

In a small series genomic alterations in tumour samples pre- and post-chemotherapy, have been correlated with likelihood of response to chemotherapy.[28] Patients with high scores for loss of heterozygosity more often had a poor response to chemotherapy than had patients with a low LOH-score. Similarly in a small study of twenty patients, global gene expression patterns or expression of a set of twenty-four genes were predictive of tumours likely to respond to Bevacizumab alone and with radiotherapy. But the role of gene changes as predictors of response while undergoing treatment was not addressed.[29]

P-glycoprotein (Pgp) is the protein product of the multidrug resistance gene MDR1. Expression of Pgp can be assessed in tumours using immunohistochemistry. While some evidence is presented that Pgp expression is associated with a worse prognosis in OS, it has not been found to be predictive of response to pre-operative chemotherapy.[30]

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2.19.2 Evidence summary and recommendations

Evidence summary	Level	References
Functional imaging such as FDG PET imaging, often in combination with	IV	

Evidence summary	Level	References
volumetric approaches (CT or MRI) can be used in assessing response to pre-operative therapy in bone and soft tissue sarcomas.		[14], [15], [31], [17], [18], [19], [20], [21], [23], [24], [25], [26], [27]

Evidence-based recommendation	Grade
Functional imaging may assist standard methods of evaluating response to pre-operative chemotherapy or radiation therapy.	**D**

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2.19.3 Issues requiring further clinical study

A gap in the evidence has been identified:

• Assessment of other in vivo methods of response monitoring is an area of clinical need. In particular, in acknowledgement of the limitations of the methods used to assess pathologic response, studies that use survival as the endpoint, rather than using the surrogate marker of pathologic response are highly desirable.

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2.20 Follow-up

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2.20.1 What is the ideal duration, frequency and modality of follow-up for BSTTs?

2.20.1.1 Introduction

Bone and soft tissue tumours (BSTTs) are a rare and heterogenous group of tumours with variable patterns of recurrence and metastasis. These characteristics make it challenging to conduct large randomised studies required to generate evidence based guidelines for follow-up/surveillance.

Ideally, routine follow-up in sarcoma patients should be conducted in a cost-effective manner that has been scientifically proven to be beneficial. Unfortunately, however, guidelines for follow-up are typically based only on opinions of international experts as there have been no valid randomised trials comparing different follow-up schedules. The best guidelines available to date come from two European consensus statements on follow-up schedules.[1][2]

Consequently there is considerable variation in the intensity, duration and modality of follow-up in BSTTs.[3] Clinical trials are needed to identify optimal surveillance strategy that balances gains in survival, quality of life, costs and societal willingness to expend resources. Current guidelines world-wide do not specify where routine follow-up should take place or who should do it.

The major goals of follow-up for BSTTs are based on early identification of potentially curable recurrences, identification of treatment related morbidity (early and late) and patient reassurance.[4] Surveillance should be based on known prognostic factors, outcomes in individual subsets and patterns of recurrence. Follow-up should be both practical and relatively cost effective.

Approximately 30-40% of all patients with BSTTs develop local or distant recurrence.[5] The risk of recurrence is greatest in the first few years with approximately two out of three of recurrences developing within two years and 95% by five years and can be stratified into risk groups, based on the prognostic features of the primary tumour.[4] However, in some subgroups, such as retroperitoneal STS and myxoid liposarcoma, late recurrence and different patterns of recurrence are more common.[4]

There is no universally accepted stopping point for tumour surveillance.

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2.20.1.2 Undertaking follow-up for local recurrence

Most local recurrences will present within five years after initial therapy.[4] Risk of local recurrence can be stratified by primary tumour characteristics and margin status.[6] Local recurrence is isolated in two thirds of patients and there appears to be benefit in to aggressive treatment of isolated first and even multiply recurrent disease.[7]

More frequent follow-up in high-risk patients has been associated with improved survival in this group with recurrent BSST by providing greater opportunities for adequate re-operation or salvage therapy.[6]

Unlike bone sarcoma, most recurrences of soft tissue sarcoma are detected by clinical examination (by clinician or patient) rather than as a consequence of routine imaging.[5] However, the ability of individual patients to detect recurrence varies. Some can identify recurrences that are not discernible to doctors, while others can be unaware of a large tumour mass.

Routine anatomical imaging should be considered for patients with resected sarcoma, particularly in settings where the primary site is difficult to examine, for example the retroperitoneum or following complex/flap reconstructions. There is a paucity of evidence guiding frequency, duration of modality of imaging in follow-up for BSTTs. Choice of CT/MRI will be guided by site (e.g. extremity versus retroperitoneum).

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2.20.1.3 Follow-up intervals and tests for local recurrence

Intervals between routine visits are mostly arbitrary, but all suggested schedules have stipulated more frequent visits for patients with more advanced disease.

Six-monthly intervals for five years and yearly thereafter are probably appropriate for patients with fully resected low risk disease, and three-monthly or four-monthly intervals for five years and yearly thereafter for patients high risk disease. These intervals are based on the consistent observation that about 80% of recurrences develop in the first five years. Lifetime surveillance has been recommended by some because late recurrences have been recorded, particularly in some subtypes, such as myxoid sarcoma.[4]

There is general consensus that the most cost-effective component of a strategy resulting in the detection of the majority of recurrences is careful history taking and physical examination.

Choice of an imaging modality in surveillance will be guided by the site (e.g. extremity versus retroeritoneum) and nature of surgical resection and/or reconstruction (e.g. metallic implants). Ultrasound, CT, PET and MRI can be useful modalities, but the relative benefit and cost-efficacy of these modalities has not been evaluated.

Very few patients have metastases identified by the routine use of imaging techniques and blood tests. There are no randomised trials indicating that such tests are of value and in any case it would be difficult to prove that the few who survive did so merely because they underwent these tests.

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2.20.1.4 Metastatic recurrence

The lung is the most common site of metastasis in patients with BSTTs.[8] The majority of pulmonary metastastic disease will present within five years after initial therapy.[9]

Surgical metastastectomy is potentially curative for pulmonary sarcoma metastases, particularly for osteosarcoma and soft tissue sarcoma. Pulmonary metastasectomy offers three year overall survival between 30-42%.[10] However, there is no consensus on a pulmonary metastatic surveillance schedule.

CT chest is a superior imaging modality to conventional chest X-ray (CXR) in identification of pulmonary metastastes at a potentially resectable stage. Two year and four year survival rates after detection of pulmonary metastsasis were 20.1% and 0% in the plain radiograph (CXR) cohort versus 47.4% and 31.6% in the CT chest ($p<0.05$).[11]

Serial monitoring with chest CT could give rise to early detection of pulmonary metastases, chance for metastastasectomy and eventually survival advantage[11] athough interpretation of data would be thwarted by possible lead-time bias.

The recommendations given below are based on the best evidence currently available, but it is acknowledged that this is low-level evidence. Individual patients may prefer more frequent follow-up for reassurance, while others may prefer less frequent follow-up because of the anxiety provided by the follow-up visits or the time and expense associated with attendance for follow-up. However, the recommendations are a reasonable compromise which, reinforced by good patient education, should ensure that most sarcoma recurrences are detected promptly and potentially resectable metastatic progression is diagnosed early.

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2.20.2 Evidence summary and recommendations

Evidence summary	Level	References
Most extremity bone and soft tissue tumour recurrences will be detected by clinical examination rather than routine imaging. The majority of local recurrences will occur within five years after resection. Risk of local recurrence can be stratified by tumour site, grade and margin status. More frequent follow-up in high-risk patients has been associated with improved survival in this group with recurrent BSTTs by providing greater opportunities for adequate re-operation or salvage therapy.	III-3, IV	[6], [5]

Evidence-based recommendation	Grade
Regular clinical examination is part of routine surveillance for local recurrence.	**D**

Practice point
Where the primary site is difficult to examine, for example the retroperitoneum or following complex/flap reconstructions routine imaging may be appropriate.

Evidence summary	Level	References
Pulmonary surveillance offers potential survival advantage. CT is superior to chest X-ray in identification of potentially resectable pulmonary sarcoma metastases There is a lack of valid prospective studies of the efficacy of routine follow-up. No study has demonstrated an improvement in survival due to intense routine surveillance. There may be some advantage in terms of patient reassurance and the detection of new metastastic progression.	III-3	[11]

Evidence-based recommendation	Grade
High risk patients in whom pulmonary metastasectomy would be considered, are advised to undergo three to six month CT chest until five years.	**D**

Practice point
Follow-up intervals recommended in current multinational guidelines are each three to four months in years one and two after diagnosis, six monthly in years three to four and annual thereafter. Late metastases may occur >10 years after diagnosis and there is no universally accepted stopping point for tumour surveillance. By contrast, the incidence of late effects of treatment increases with time. For patients enrolled in clinical trials, the above recommendations may vary in accordance with the follow-up protocols of these trials.

Practice point

For patients considered suitable for pulmonary metastasectomy, low dose protocol non- contrast CT chest is the modality of choice for pulmonary surveillance.

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2.20.3 Issues requiring more clinical research study

• What is the most cost effective imaging modality and surveillance interval for patients with resected sarcoma?

• What is the appropriate frequency of pulmonary surveillance for patients at differing risk of pulmonary metastases?

• What is the role of PET in long-term interval surveillance for resected sarcoma?

• What is the optimal duration of imaging surveillance in different risk groups?

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2.21 Guideline development process

2.21.1 Guideline development process

2.21.1.1 Introduction

Cancer Council Australia (CCA) have collaborated with the Australasian Sarcoma Study Group (ASSG) to develop Clinical Practice Guidelines for the Management of Adult Onset Sarcoma. The establishment of these guidelines presents a historic opportunity for the sarcoma community, which deals with a small orphan cancer which suffers from fragmented patterns of care based around State and Centre orientations and philosophies, and consequently results in a significant variation in the way clinicians manage the disease.

The guidelines were developed by a multidisciplinary working group (see Guideline Working Party members). Topic leaders from the Working Party membership were designated to address topics in their areas of expertise, with other Working Group members contributing as co-authors. The literature assessed for these guidelines focuses on adult patients with sarcoma. Future iterations of the guidelines will also include paediatric and gynaecological topics.

The guideline development process, conducting the literature searches, appraising the literature and formulating and grading recommendations, followed the guideline development process outlined below.

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2.21.1.2 Steps in preparing clinical practice guidelines

A clear strategy was developed and each topic author followed the appropriate steps in preparing their guideline sections. The Working Party developed clinical questions and topic groups were assigned to review and synthesise the relevant literature and to formulate evidence-based recommendations. The search strategy and literature search was conducted by the Project Officer, who distributed the search results to the Working Party authors. The strategic steps followed are outlined below:

1. Structure the research questions
2. Develop a search strategy
3. Search the literature
4. Critically appraise the literature
5. Formulate and grade recommendations

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2.21.1.3 Structure the research questions

The Working Party discussed the most important aspects of the management of Sarcoma and developed clinically focussed key questions. These questions were developed and approved by Working Party members. The clinical questions asked for the Management of Sarcoma guidelines, are as follows:

2.21.1.4 Diagnosis

- What are the relative rates of efficacy and accuracy of various biopsy modalities in bone and soft tissue tumours?
- What are the most appropriate imaging modalities for diagnosis and staging of bone and soft tissue tumours?
- What is the impact of delay in referral to a specialist centre in bone and soft tissue tumours?

2.21.1.5 Multidisciplinary Treatment

- What is the role of prognostic factors in management of BSTTs?
- What is the outcome of a second opinion in BSTT pathology?
- Does referral to a specialist centre improve outcomes in BSTTs?

2.21.1.6 Chemotherapy (systemic therapies)

- What is the role for adjuvant systemic therapy for adults with BSTT?
- What is the role for systemic therapy in advanced soft tissue sarcoma?

2.21.1.7 Radiotherapy

- What is the evidence for radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage?
- What is the evidence that pre-operative radiotherapy is superior to post-operative radiotherapy in limb and extremity soft tissue sarcoma in terms of local recurrence, survival and limb salvage and morbidity?
- What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in truncal sarcomas?
- What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence or improves survival in retroperitoneal sarcomas?
- What are the indications for IMRT, brachytherapy, intraoperative radiotherapy (IORT), extra-corporeal radiotherapy and particle therapy in the management of BSTTs?

2.21.1.8 Surgery

- What are the factors influencing the extent of surgery in BSTTs?
- What are the factors that impact on the choice of reconstructive options in BSTTs?
- What preoperative optimisation strategies improve outcomes in BSTTs?
- What is the role of regional chemotherapy in BSTTs?

2.21.1.9 Follow-up

- What are the measures to assess treatment response in BSSTs?
- What is the ideal duration, frequency and modality of follow-up for BSTTs?

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2.21.1.10 Develop a search strategy

Appropriate search strategies were constructed for each clinical question. MeSH terms were agreed by the Working Party members and were expanded by the Project Officer after conducting pilot searches and searching the MeSH vocabulary. MeSH index terms were translated to Emtree terms for the Embase database to ensure that appropriate index terms unique to each database were used. When there was no appropriate MeSH or Emtree index term available a combination of free text words were used in order to capture the relevant data.

The following exclusion criteria was applied: studies published pre 1990, languages other than English, and the following study designs: non-systematic reviews, case reports, letters, editorials, comments, animal, in vitro and laboratory studies. This exclusion criteria was then refined as per individual clinical question. The search strategy was approved by the members of the Working Party.

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2.21.1.11 Search the literature

A range of medical databases, guideline clearinghouses and clinical trial portals were searched. These included The Cochrane Library, PubMed, Embase, Trip Database, the National Guideline Clearinghouse, the National Comprehensive Cancer Network, ClinicalTrials.gov, and the National Institute for health and clinical excellence. Search results were screened for relevance by the Project Officer and relevant literature was collated, the full text articles obtained and sent to Working Party topic authors to critically appraise, synthesise and use as the evidence base for their topic questions. To view the complete search yield and more detailed information about the literature search such as inclusion and exclusion criteria, please go to each clinical question page. The information can be found in the Appendices on each question page.

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2.21.1.12 Critically appraise the literature

Relevant articles selected from the literature search were reviewed by the clinical question authors and each article was critically appraised with respect to level of evidence, quality of the evidence, size of the effect and clinical importance and relevance. Level of evidence was assigned according to the following criteria from the NHMRC Evidence Hierarchy:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a	A prospective cohort study	A prospective	A randomised controlled trial

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
		defined clinical presentation		cohort study	
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study ■ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study
III-3	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study ■ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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2.21.1.13 Formulate and grade recommendations

The body of literature was assessed by each topic author and recommendation grades were assigned using the following criteria adapted from the NHMRC body of evidence matrix:

Component of Recommendation	Recommendation Grade			
	A Excellent	**B Good**	**C Satisfactory**	**D Poor**
Volume of evidence [1**]	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or a systematic review /several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies /systematic reviews with a high risk of bias
Consistency [2**]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

[1] Level of evidence determined from level of evidence criteria

[2] If there is only one study, rank this component as 'not applicable'

[3] For example results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

[**] For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B!

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Recommendation grades are indicated below:

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Adapted from: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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2.21.1.14 Write the topic

Topic authors were asked to write the content for their guideline question topic using the following format:

- background
- review of the evidence
- evidence summary with levels of evidence and numbered references
- recommendation(s) and corresponding grade(s)
- references

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2.21.1.15 Review of the question topics

The body of evidence and recommendations for each question topic were reviewed by the Guidelines Working Party and final recommendations agreed to, based on the evidence.

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2.21.1.16 Public consultation

The draft guidelines were released for public consultation to all interested parties in Australia for the period from 3 September to 3 October 2013. The consultation process involved soliciting public review of the draft guidelines through posting onto the Cancer Council Australia Cancer Guidelines Wiki and alerting professional societies and other interest groups via link to the site. All feedback on the draft received during the consultation period in Australia was reviewed by the topic authors and Guidelines Working Party. Subsequent changes to the draft was agreed by consensus of the Guideline Working Party, based on consideration of the evidence.

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2.21.2 References

<references>

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1. ↑ [1.0] [1.1] [1.2] National Health and Medical Research Council. *NHMRC Australian Guidelines to reduce health risks from drinking alcohol.* Commonwealth of Australia: National Health and Medical Research Council; 2009 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ds10-alcohol.pdf.

2.22 Working party members

Working party members and contributors

Working party member	Clinical questions
Assoc Prof Chris Hemmings	
Associate Professor Gelareh Farshid	
Associate Professor Sam Ngan, MBBS, FRCSE, FRANZCR	
Associate Professor Susan Neuhaus	
Dr Annabelle Mahar	
Dr Fiona Bonar	
Dr Fiona Maclean	
Dr Grant Pang	
Dr Jayesh Desai	
Dr Julie Chu	
Dr Kirsten Gormly	
Dr Marcus Foo FRANZCR	
Dr Mark Wilsher	
Dr Michael Dray, FRCPA	
Dr Paul Stalley	
Dr Raghu Gowda MSc MD MRCP(UK) FRCR(UK) FRANZCR	
Dr Richard Boyle FRACS FA(Orth)A	

Working party member	Clinical questions
Dr Roger Woods MBBS, FRACS	
Dr Sarat Chander FRANZCR	
Dr Steve Chryssidis	
Dr Warren Hargreaves	
Professor David Thomas FRACP, PhD	
Professor Martin Tattersall SCD, MD FRACP	
Professor Peter Choong FRACS, FAOrth A, MBBS MD	

Name	Affiliation
Dr Mandy Ballinger	Working Party member, Peter MacCallum Cancer Centre, VIC
Marianne Griffin	Working Party member, Oncology Nurse, VIC
Dr Helen Irving	Working Party member, Paediatric Oncologist, Royal Children's Hospital, QLD
Dr Jonathan Karpelowsky	Working Party member, Paediatric Surgeon, The Children's Hospital at Westmead NSW
Dr Geoffrey McCowage	Working Party member, Paediatric Oncologist, The Children's Hospital at Westmead NSW
Dr Gillian Mitchell	Working Party member, Clinical Oncologist, Peter MacCallum Cancer Centre, VIC
Dr Marianne Phillips MBCHB, FRCP, FRCPCH, FRACP	Working Party member, Consultant Paediatric and Adolescent Oncologist, Princess Margaret Hospital for Children, WA
Leigh Webb (QLD)	Consumer representative to the Working Party

2.23 Conflict of interest register

Competing interest declarations and management

Working Party Members were asked to declare in writing, any interests relevant to the guideline development, prior to commencement. Members were asked to update their information if they became aware of any changes to their interests.

All declarations were added to a register of interests as listed below. The register was made available to the Working Party throughout the development of the guideline, allowing members to take any potential conflicts of interest into consideration during discussions, decision making and formulation of recommendations.

If Working Party Members were identified as having a significant real or perceived conflict of interest, the Chair could decide that the member either leave the discussion whilst the specific area they were conflicted in was discussed or the member could remain present but not participate in the discussion, or decision making on the specific area where they were conflicted. There were no instances where this occurred during the development of this guideline.

Working party member	Competing interest declaration
Assoc Prof Chris Hemmings	No competing interest to declare.
Associate Professor Gelareh Farshid	No competing interest to declare.
Associate Professor Sam Ngan, MBBS, FRCSE, FRANZCR	No competing interest to declare.
Associate Professor Susan Neuhaus	Board of Directors, Cancer Council South Australia (CCSA) Board of Directors, Australasian Sarcoma Study Group (ASSG)
Dr Annabelle Mahar	No competing interest to declare.
Dr Fiona Bonar	No competing interest to declare.
Dr Fiona Maclean	No competing interest to declare.
Dr Grant Pang	To be confirmed
Dr Jayesh Desai	Shares: NIL Research Support: Novartis, Pfizer, Roche, GSK, Plexxikon Consultancy: Novartis, Pfizer, GSK, Merck Serono, Sanofi, Bionomics, Circadian
Dr Julie Chu	No competing interest to declare.
Dr Kirsten Gormly	No competing interest to declare.

Working party member	Competing interest declaration
Dr Marcus Foo FRANZCR	No competing interest to declare.
Dr Mark Wilsher	No competing interest to declare
Dr Michael Dray, FRCPA	No competing interest to declare.
Dr Paul Stalley	TBC
Dr Raghu Gowda MSc MD MRCP(UK) FRCR(UK) FRANZCR	No competing interest to declare.
Dr Richard Boyle FRACS FA(Orth)A	No competing interest to declare.
Dr Roger Woods MBBS, FRACS	No competing interest to declare.
Dr Sarat Chander FRANZCR	No competing interest to declare.
Dr Steve Chryssidis	No competing interest to declare.
Dr Warren Hargreaves	No competing interests to declare
Professor David Thomas FRACP, PhD	No competing interests to declare with respect to the matters contained in these guidelines. Received sponsorship to attend meetings and research support from Amgen, Pfizer and Novartis.
Professor Martin Tattersall SCD, MD FRACP	No direct pecuniary interest to declare. Attended an investigator meeting in Seoul and Los Angeles related to trials of new drugs in chondrosarcoma and soft tissue sarcoma. The flight and accommodation was covered by the sponsoring company.
Professor Peter Choong FRACS, FAOrth A, MBBS MD	Prosthetic design team, Zimmer Corporation, USA for which travel and accommodation costs and past royalties have been paid. Instrument design team, Johnson & Johnson, USA for which travel and accommodation costs, and per diem have been paid. ARC Linkage grant with industry partner, Johnson & Johnson

2.24 Abbreviations

Abbreviations

3-DCRT	3-D Conformal Radiotherapy
ALK	Anaplastic lymphoma kinase
ASPS	Alveolar soft-part sarcoma
AYA	Adolescent and young adult
BMI	Body mass index
COL1A1	Collagen, type I, alpha 1
CSS	Cause specific survival
CT scan	Computed tomography
CXR	Conventional chest X-ray
DFSP	Dermatofibrosarcoma protuberans
DSS	Disease specific survival
DVT	Deep vein thrombosis
EBRT	External beam radiotherapy
ERB2	Human Epidermal growth factor Receptor 2
ESTS	Extremity soft tissue sarcoma
FDG	18F-fluorodeoxyglucose
FDG PET	Fluorodeoxyglucose positron emission tomography
FNA	Fine needle aspiration
FNCLCC	French Federation of Cancer Centers Sarcoma Group
GIST	Gastrointestinal stromal tumour
GP	General practitioner
H&E stain	Hematoxylin and eosin stain
HR	Hazard ratio
ILI	Isolated limb infusion
ILP	Isolated limb perfusion
IMRT	Intensity modulated radiation therapy
IVC	Inferior vena cava
IORT	Intra operative electron beam therapy
ISoLS	International Society of Limb Salvage
KIT	Kinase inhibitor therapy
MDR1	Multidrug resistance gene
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging

MRV	Magnetic resonance venography
MSKCC	Memorial Sloan-Kettering Cancer Center
MSTS	Massive soft tissue sarcoma or Musculoskeletal Tumour Society Rating Scale
mTOR	Mammalian target of rapamycin
NCB	Needle core biopsy
NCI	National Cancer Institute (United States)
OS	Overall survival
PDGF	Platelet-derived growth factor
PDGFB	Platelet-derived growth factor subunit
PEComa	Perivascular epithelioid cell tumour
PET-CT	Positron emission tomography computed tomography
PET scan	Positron emission tomography
Pgp	P-glycoprotein
PNET	Primitive Neuroectodermal Tumour
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
RNL	Reintegration to Normal Living Index
RT	Radiotherapy
STS	Soft tissue sarcoma
SUV	Standard uptake value
TESS	Toronto Extremity Salvage Score
TSC1/TSC2	Tuberous sclerosis complex
WHO	World Health Organisation
WBBS	Whole body bone scan