Clinical practice guidelines for the management of adult onset sarcoma

In collaboration with

1 Clinical practice guidelines for the management of sarcoma

1.1 Contents

1.2 Foreword

1.3 Summary of recommendations

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?
- What defines high-risk populations for bone and soft tissue tumours?

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?

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?

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 o improves survival in truncal sarcomas?
- What is the evidence that radiotherapy, either pre-operative or post-operative, decreases local recurrence o improves survival in retroperitoneal sarcomas?
- What are the indications for IMRT, 3D CRT, brachytherapy, extra-corporeal radiotherapy and proton therapy in the management of BSTTs?

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?

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?

1.10 Appendices

Guideline development process

Working party members and contributors

Conflict of interest register

Abbreviations

1 Foreword

Foreword

2 Summary of recommendations

2.1 Summary of recommendations

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 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**
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**

Recommendation	Grade
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	**B**

Recommendation	Grade
local control over surgery alone for high grade sarcomas for the limb and trunk.	
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**
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**

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 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.

Point(s)
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**
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	

Recommendation	Grade
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 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-	**D**

Recommendation	Grade
operative chemotherapy or radiation therapy.	

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 /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
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	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
	some other method)	non-consecutive patients with a defined clinical presentation			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
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)

Back to top

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Back to top

2.1 Impact of referral delay

Contents

2.1.1 What is the impact of delay in referral to a specialist centre in bone and soft tissue tumours?

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 >3 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: 10 years in one extreme example, [3] but more often from a few months [5] to around a year. [3][4]

Back to top

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 "nonrepresentative 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]

Back to top

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 >3 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]

Back to top

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**

Evidence-based recommendation
Any tumour mass greater than 5cm deep or attached to the deep fascia should be considered a sarcoma until proven otherwise.

Practice point

If sarcoma is suspected then immediate referral to a specialist sarcoma unit is good practice.

Back to top

2.1.3 Issues requiring more clinical research study

A gap in the evidence has been identified to include:

- What are the barriers to diagnosis and treatment and their impact on patients' prognosis?

Back to top

2.1.4 References

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Back to top

2.1.5 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

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 bone and soft tissue tumours?

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 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 bone and soft tissue tumours, 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]

Back to top

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]

Back to top

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]

Back to top

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 bone and soft tissue lesions, but this may depend on site, with one study reporting only 33% accuracy in abdominal wall tumours.[19] 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 bone and soft tissue tumours 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 bone and soft tissue tumours 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.

Back to top

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**

Back to top

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Back to top

2.2.4 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

2.3 Imaging modalities

2.3.1 What are the most appropriate imaging modalities for diagnosis and staging of bone and soft tissue tumours?

2.3.2 References

Back to top

2.3.3 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

2.4 Sentinel node biopsy

2.4.1 Background

2.4.2 Evidence summary and recommendations

2.4.3 References

Back to top

2.5 Prognostic factors

Contents

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] 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.[7][8][5][9][10] 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.[11][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.[12] 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).

Back to top

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.[13][14][15] 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 tumor size, excision margin, ablative surgery, age, male sex, serum alkaline phosphatase level, local recurrence, p-glycoprotein expression, and Erb2 expression.[16]

Back to top

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.[17] All of these tumours are rare and Ewing's tumours of bone make up approximately 3% of all paediatric malignancies.[18][19][20]

Back to top

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.[21][12][22][10][6]

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.[23][24][25] 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.

Back to top

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], [11], [26], [27], [28], [29], [30], [31], [32], [6], [33]
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	[27], [16], [34], [13], [15], [14], [35]

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	[36], [37], [38], [39], [18], [40], [17], [20], [19]
It is unusual 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.	IV	[28], [41], [11], [26], [2], [42], [8], [43], [7]
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 disease specific survival. Outcomes may be better when patients are treated in specialised centres.	IV	[26], [44], [28], [45], [29], [43], [30], [27], [46], [47], [31]
For truncal tumours, tumour grade, excision margins, tumour size and the use of radiotherapy influence local and distant recurrence.	IV	[26], [25], [48], [30], [49], [33], [41]
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 5-fold increase in death. As yet there is no evidence that neo-adjuvant therapies improve disease-specific survival. There is some evidence that only tumour grade remains a significant prognostic factor one year after diagnosis.	IV	[12], [6], [23], [26], [25], [50], [2], [11], [1], [42], [51], [52], [53], [54], [55], [56], [57], [58], [24]
For tumours of the head and neck, excision margins influence local recurrence. Tumour grade and patient age influence overall survival.	IV	[59], [60], [61], [62], [63], [64], [65], [66], [61], [67], [68], [69]

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.

Back to top

2.5.3 References

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Back to top

2.5.4 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

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 are collectively uncommon and individually comprise many rare entities, pathologists outside specialist sarcoma centres 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 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.

Back to top

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]

Back to top

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.

Back to top

2.6.2 Evidence summary and recommendations

Evidence summary	Level	References
Expert review of bone and soft tissue tumours 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**

Back to top

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Back to top

2.6.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search
View PICO				

2.7 Referral to specialist centre

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

2.7.2 References

Back to top

2.7.3 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search
View PICO				

2.8 Adjuvant systemic therapy

Contents

2.8.1 What is the role for adjuvant systemic therapy in 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 primary or neo-adjuvant chemotherapy may also provide important prognostic information, enabling informed treatment decisions after completion of local treatment.

Back to top

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.

Back to top

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

Back to top

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

Back to top

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 preoperative chemotherapy predicts survival.	II	[2]

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

Evidence-based recommendation	Grade
Intra-arterial chemotherapy compared to intravenous administration has not been shown to improve outcome.	**B**

Evidence summary	Level	References
Altering post-operative chemotherapy in poor responders to primary chemotherapy has not been shown to improve outcomes.	II	[3]

Evidence-based recommendation	Grade
Primary chemotherapy including cisplatin, doxorubicin and high dose methotrexate improves outcomes compared to regimens omitting high dose methotrexate. 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.	**B**

Malignant fibrous histiocytoma of bone

Evidence summary	Level	References
Doxorubicin and cisplatin neoadjuvant 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
Doxorubicin and cisplatin are a reasonable primary treatment.	**D**

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

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

Evidence-based recommendation	Grade
Doxorubicin and cisplatin are reasonable primary treatment.	**D**

Ewings sarcoma

Evidence summary	Level	References
All current trials of treatment employ primary 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 60-70% in those with localized 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
Most combination chemotherapy regimens include vincristine, dactinomycin, cyclophosphamide, ifosfamide, doxorubicin and etoposide. Treatment given every two weeks is more effective but more toxic than three weekly treatments.	**B**

Soft Tissue Sarcomas

Evidence summary	Level	References
Adjuvant chemotherapy with doxorubicin in localized resectable soft tissue sarcoma reduces distant and overall recurrence OR 0.7 (95% CI 0.56-0.82; p=0.0001).	I, II	[7], [8]
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]

Evidence-based recommendation	Grade
The odds ratio for local recurrence was 0.73 (95% CI 0.56-0.94; p=0.02) in favour of doxorubicin. In terms of survival, doxorubicin alone had an OR of 0.84 (95% CIn0.68-1.03; p=0.09).	**C**

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

Evidence-based recommendation	Grade
The use of neo-adjuvant chemotherapy in adult type soft tissue sarcomas is not the standard of care.	**C**

Back to top

2.8.3 References

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Back to top

2.8.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search
View PICO				

2.9 Systemic therapy

Contents

2.9.1 What is the role for systemic therapy in advanced BSTT?

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.

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. 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 with clinical activity in advanced soft-tissue sarcomas, such as trabectedin and pazopanib, are not yet approved by the Therapeutic Goods Administration for this indication (trabectedin), or are not reimbursed by the Pharmaceutical Benefits Scheme (both agents).

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.

2.9.1.2 Specific soft-tissue sarcoma subtypes

The development of KIT and other kinase-directed inhibitors for gastrointestinal stromal tumours 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 STS given the treatment implications.

Back to top

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	[3], [4], [5], [6]

Evidence-based recommendation	Grade
There is no evidence to support more aggressive regimens in the first line treatment of advanced soft-tissue sarcomas.	**A**

Evidence summary	Level	References
For patients in whom doxorubicin is considered inappropriate (for example, for patients who have received doxorubicin as part of adjuvant or neoadjuvant therapy,	II	[7], [8]

Evidence summary	Level	References
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.		
For patients with uterine leiomyosarcoma, the combination of docetaxel and gemcitabine may be considered in first line.	III-1, IV	[9], [10]

Second line

Evidence summary	Level	References
For patients who have not received ifosfamide as first line, single agent ifosfamide.	II	[8], [11]
For patients with myxoid liposarcoma or leiomyosarcoma, consideration may be given to trabectedin.*	II	[12], [13], [14], [15]

Evidence-based recommendation	Grade
For patients who have not received ifosfamide as first line, single agent ifosfamide.	**B**

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

Third line

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	[16]
The antiangiogenic agent, pazopanib*, was superior to placebo in progression-free but not overall survival.	II	[17]

- Pazobpanib is not reimbursed in Australia for soft-tissue sarcoma.

2.9.2.2 Specific soft-tissue sarcoma subtypes

Evidence summary: 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. **Ref: Mcarthur 2005, level 3 evidence**

Evidence summary: 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.**Ref: Wagner 2010, level 3 evidence Evidence summary:**Inflammatory myofibroblastic tumors are associated with transolcations of anaplastic lymphoma kinase (ALK) in approximately 50% of cases; activity has been reported with the ALK inhibitor crizotinib.**Ref: Butrynski 2010, level 3 evidence**

Evidence summary	Level	References
Although not characterised molecularly, angiosarcomas need to be considered as a distinctive soft tissue subtype, and treated accordingly. 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 that 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	[18]

Back to top

2.9.3 References

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Back to top

2.9.4 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO

2.10 Radiotherapy in STS

Contents

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). Preoperative or postoperative RT and 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

There is level II evidence that postoperative 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.

There is also level II evidence that local control was similar in both the preoperative RT and postoperative RT group.[2]

Postoperative brachytherapy has been shown to improve local control in high grade STS after complete resection in a number of randomised controlled trials.[3][4][5]

There is level IV evidence that intraoperative or perioperative brachytherapy in combination with external beam radiotherapy following re-resection may improve local control rate in patients with recurrent sarcoma.

There is level IV evidence that post-operative radiotherapy improves local control rate for extremity STS with positive margins.[6]

There is insufficient evidence to suggest altered fractionation schedules compared to conventional fractionated radiotherapy of 1.8-2Gy fractions.

There is no evidence that the addition of radiosensitizer to post-operative radiotherapy improves local control.[7]

Back to top

2.10.1.3 Evidence for radiotherapy in terms of survival

Randomised studies for postoperative radiotherapy or brachytherapy following limb sparing surgery did not demonstrate any survival benefit.

There is, however, level IV evidence from a SEER analysis by Koshy et al, 2010[8] that a statistically significant improvement in overall survival (OS) in patients with high grade extremity STS who received radiotherapy (3yr OS 73% vs 63%) was demonstrated.

Another SEER analysis by Schreiber et al, 2012[9] reported an improved OS and disease specific survival (DSS) for patients with tumours >5cm who had post-operative radiotherapy after limb sparing surgery.

Back to top

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 postoperative radiotherapy compared with those managed with amputation. (Rosenberg et al, 1982).

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

Back to top

2.10.2 Evidence summary and recommendations

Back to top

2.10.3 References

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Back to top

2.10.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.11 Pre-operative radiotherapy

Contents

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 preoperative setting has been reported in multiple retrospective series. To date, there has only been one randomised controlled trial comparing preoperative and postoperative 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 preoperative radiotherapy (50Gy) vs postoperative radiotherapy (66-70Gy), with major wound complications being the primary endpoint. Patients whom received preoperative radiotherapy had a significantly higher rate of major wound complications compared with patients receiving postoperative radiotherapy (35% vs 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 preoperative 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 **[ref]** and confirmed ongoing equivalence of local control between the two arms (93% vs 92%), and similar overall survival (73% vs 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 preoperative and postoperative arms, respectively. A greater proportion of patients in the postoperative 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 preoperative 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 5 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 vs. 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.

Maybe also should mention a number of retrospective studies reported the use of higher radiation dose, as used in the post-operative setting is associated with inferior functional outcomes and more chronic radiation related complications.

Theoretical advantages of pre-operative radiotherapy should also be mentioned.

2.11.2 Evidence summary and recommendations

Evidence summary	Level	References
There is no significant difference in local control or survival between preoperative and postoperative radiotherapy in localised resectable ESTS.	II	[2], [5]
Preoperative radiotherapy increases the rate of wound complications, following limb-sparing surgery for ESTS.	II	[2]
Postoperative radiotherapy may increase the rate of long-term radiation toxicity including subcutaneous fibrosis, edema and joint stiffness.	II	[6]

Practice point
Preoperative radiotherapy may be the preferred approach in certain situations such as: A tumour of borderline resectability, and preoperative 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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Back to top

2.11.4 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

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 MSKCC spanning over a period of forty years looking at 189 patients, the authors reported overall 5 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.

Back to top

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]

Back to top

2.12.1.4 Preoperative vs Postoperative Radiotherapy

As with extremity sarcomas, there are benefits with preoperative RT compared with postoperative RT such as:

- The main advantage of preoperative RT is that the gross tumor volume can be precisely defined for radiation treatment planning, allowing accurate targeting of the radiation volume around the tumor.
- The tumor 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 tumor are less likely compared to the postoperative setting.
- The risk of intraperitoneal tumor dissemination at the time of the operation may be reduced by preoperative RT.
- Radiation is considered to be biologically more effective in the preoperative setting.
- It is possible that an initially unresectable tumor may be converted to one that is potentially resectable for cure.

Back to top

2.12.1.5 Newer radiotherapy techniques

There is some evidence that newer RT techniques such as Intra operative 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 Retroperitoneal Sarcomas (RPS) but still in early stages and may take some time for results to come.

Back to top

2.12.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients presenting with non-metastatic truncal sarcomas, improved local control is seen with adding radiation therapy to surgery. Preoperative radiotherapy is preferable. Evidence regarding radiotherapy benefit in improving overall survival is not clear.	III-2, IV	[3], [4]

Evidence-based recommendation	Grade
In patients with non-metastatic truncal sarcomas, adding radiotherapy to surgery is appropriate to further improve local control. Preoperative radiotherapy with its additional benefits is preferable.	**C**

Back to top

2.12.3 References

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Back to top

2.12.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.13 Radiotherapy in retroperitoneal sarcomas

Contents

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.

Back to top

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.

Back to top

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.

Back to top

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**

Back to top

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.

Back to top

2.13.4 References

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Back to top

2.13.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.14 Comparison: Types of radiotherapy

2.14.1 What are the indications for IMRT, 3D CRT, brachytherapy, extra-corporeal radiotherapy and proton therapy in the management of BSTTs?

2.14.2 References

Back to top

2.14.3 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.15 Factors influencing surgery extent

Contents

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 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 endoprosthesis 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.

Bone and soft tissue tumours 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.

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Any lump greater than 5 cm or deep to the deep fascia should be considered a sarcoma until pr

Persistent and unremitting pain, unresponsive to oral analgesia and nocturnal in occurrence s
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- **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.
- **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.

Back to top

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.

Back to top

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.

Back to top

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 neoadjuvant or adjuvant 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 chose 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]

Back to top

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 randomized prospective phase III trial of combined chemotherapy radiotherapy for high risk soft tissue sarcoma demonstrated that administration of preoperative therapies minimized 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.

Back to top

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]

Back to top

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.

Back to top

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]

Back to top

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.

Back to top

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]

Back to top

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.	IV	[3], [26], [27], [28], [29]

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

Unplanned excision

Evidence summary	Level	References
Unplanned excision with positive margins results in higher incidence of local recurrence. 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	[30], [13], [12], [31], [14]

Evidence-based recommendation	Grade
Musculoskeletal tumours are best managed in a specialized tumour centre by a multidisciplinary unit.	**C**

Retroperitoneal sarcoma

Evidence summary	Level	References
The single most important factor affecting the ability to remove the primary tumour completely was multiple organ involvement. Aggressive surgery carried out in a specialised tumour centre is safe and is associated with improved local control.	III-3, IV	[32], [33], [34], [35], [36]

Evidence-based recommendation	Grade
Retroperitoneal sarcomas can be extensive and involve multiple organs. Good results can be achieved but require an aggressive approach. This is best managed in a specialised tumour centre by a multidisciplinary unit.	**C**

Limb salvage surgery in Osteosarcoma

Evidence summary	Level	References
LLS has higher rates of survival and lower secondary amputation.	III-3	[37], [38]

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

Radiotherapy in sarcoma

Evidence summary	Level	References
Epineural dissection in conjunction with preoperative radiotherapy is a safe and effective technique to preserve vital nerves.	III-2	[39]

Evidence-based recommendation	Grade
Preoperative radiation therapy allows preservation of vital structures without compromising local control.	C

Evidence summary	Level	References
Radiotherapy is an important adjunct to the management of STS and reduces the risk of local recurrence.	III-3, IV	[40], [23], [41], [42]

Evidence-based recommendation	Grade
Pre or post-operative radiation therapy should be considered in the management of soft tissue sarcoma. It has been shown to reduce the risk of local recurrence. Decision should be made in the setting of a multidisciplinary team.	C

Isolated limb perfusion

Evidence summary	Level	References
ILF can be effective in facilitating limb preservation surgery.	III-3, IV	[43], [44], [45], [46]

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
Gd 1 chondrosarcoma can be treated with intralesional excision safely.	III-3, IV	[47], [18], [48]

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

Mohs micrographic surgery

Evidence summary	Level	References
Mohs micrographic surgery (MMS) is a safe technique in the management of DFSP but requires institutional expertise.	III-3, IV	[49], [50], [51]

Evidence-based recommendation	Grade
Mohs micrographic surgery (MMS) is an acceptable technique in the management of dermatofibrosarcoma protuberans (DFSP). It requires substantial expertise and should be done in an appropriate institution.	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 stimulated 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 minimize the impact of biopsy induced image artifact.

Practice point

Sarcomas should be managed at a tumour centre.

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 tumour are large and excised with marginal margins.

Practice point

Soft tissue sarcomas excised outside a tumour centre have a high risk of residual disease and positive margins. These tumours should be re-excised with wide margins and treated with adjuvant radiotherapy.

Back to top

2.15.3 References

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Back to top

2.15.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

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.

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 bony reconstruction
- Treatment related factors
  - Peri-operative chemotherapy
  - Peri-operative radiotherapy

Back to top

2.16.1.2 General principles of reconstruction in sarcoma

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

- Patient general optimization
  - Nutrition
  - Minimise smoking
  - Diabetic control
  - General complication reduction (DVT prophylaxis, chest physio, peri-operative antibiotics etc)
- 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]

Back to top

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 neo-adjuvant 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 neo-adjuvant and adjuvant radiotherapy, neo-adjuvant 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 adjuvant and neo-adjuvant radiotherapy in development of complications, suggested adjuvant radiotherapy may lead to a higher rate of complications than neo-adjuvant 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 neo-adjuvant radiotherapy to reduce the risk of wound complications. [6] When neo-adjuvant 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 neo-adjuvant 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 adjuvant 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 minimize 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. These techniques are reliable and effective in the reconstruction of both bony and soft tissue defects. [14] [15] [16] [17]
- 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]

Back to top

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). [21]

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. [22] [23] [24] [25] [26] [27] [28] [29] [30] 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.[31]

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. [32]
- Bone that has undergone extracorporeal irradiation has also been successfully used. [33] [34]
- Prosthetic (metallic) intercalary reconstruction.
- Sometimes combinations of the above are used. **Stalley and Muscolo ref** [35] [36] [37]

Periarticular reconstruction

EndoProsthetic reconstruction has been shown to have acceptable oncological and functional results **Harn and Kawal ref**[38] [39] [40] [41] [42] [43] [44] [36] [45] in setting of pathological fracture. [46] [47] [24]

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

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).**Stanmore group and Schiller ref** [48] [49] [38]

Back to top

2.16.2 Evidence summary and recommendations

Evidence summary	Level	References
Improved patient outcome with extremity soft tissue sarcoma if patient is better educated, optimistic, with lower baseline health-related quality of life.	III-3	[1]

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 may be better managed in a specialized referral centre 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 adjuvant 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 neoadjuvant 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]
Neo-adjuvant radiotherapy leads to a higher wound complication rate in comparison to adjuvant radiotherapy.	II	[6]
Adjuvant radiotherapy may lead to a greater complication profile in comparison to neo-adjuvant radiotherapy in treatment of sarcoma.	III-2	[7]

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

Evidence summary	Level	References
Reconstruction of sarcoma defects treated with neo-adjuvant radiotherapy is more	III-2	[8]

Evidence summary	Level	References
effective when vascularised flap closure is used, particularly free tissue transfer.		
Neo-adjuvant radiotherapy leads to a greater use of vascularised flap coverage of soft tissue sarcoma defects.	II	[6]
Following neoadjuvant 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 neo-adjuvant radiotherapy.	**B**

Evidence summary	Level	References
Vascularised soft tissue coverage after resection of extremity soft tissue sarcomas is resilient when treated with adjuvant 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 adjuvant 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.	IV	[14]
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 neo-adjuvant radiotherapy.	IV	[15]
Vascularised soft tissue coverage of upper limb soft tissue defects after sarcoma resection is safe and effective.	IV	[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	IV	[18]

Evidence summary	Level	References
by a specialist team for best functional outcome.		

Evidence-based recommendation	Grade
Recommend specialist referral for management of reconstruction of forearm and hand sarcomas.	**D**

Chest wall

Evidence summary	Level	References
Reconstruction of chest wall sarcoma defects with polypropylene mesh and pedicled latissimus dorsi flap is safe and effective.	IV	[20]

Evidence-based recommendation	Grade
Consider use of polypropylene mesh with flap coverage in reconstruction of chest wall defects following sarcoma resection.	**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 microsurgical 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

Reconstruction in the growing skeleton requires additional expertise, and consideration should be made to use a growing prosthesis in this group when physeal resection is required.

Practice point

Reconstruction of specific areas may require site-specific specialists. A specialist Hand and Upper limb surgeon should be consulted for resection and reconstruction in the hand and forearm for best outcome in this critical functional area.

Back to top

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.

Back to top

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Back to top

2.16.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.17 Preoperative optimisation strategies

Contents

2.17.1 What preoperative optimisation strategies improve outcomes in BSTTs?

2.17.1.1 Introduction

A number of preoperative 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 neo-adjuvant therapies

2.17.1.2 Preoperative embolisation of bone neoplasms

A limited number of publications describe the use of gelatin microspheres or polyvinyl alcohol particles as preoperative 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 RCTs have been conducted comparing the use of embolisation with either no-preoperative intervention or with an alternate modality.

2.17.1.3 Preoperative embolisation in retroperitoneal sarcoma

Preoperative 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 Preoperative 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 neo-adjuvant 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 preoperative embolisation in selected cases may decrease operative blood loss and facilitate surgical resectability.	III-3, IV	[1], [2]

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

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

Evidence-based recommendation	Grade
Neo-adjvuant imatinib mesylate may be considered in selected patients when surgery is difficult or potentially mutilating.	**D**

Practice point
It is advisable to consider the suitability and applicability of preoperative 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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Back to top

2.17.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.18 Regional chemotherapy

Contents

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 neo-adjuvant 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.

Back to top

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

No RCT or other comparative study was available comparing ILP with other treatment options (e.g. neo-adjuvant or amputation) for locally unresectable 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]

Back to top

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.

Back to top

2.18.2 Evidence summary and recommendations

Evidence summary	Level	References
Isolated limb perfusion is an effective limb-sparing option for patients with unresectable soft tissue sarcoma, as an alternative to amputation.	III-3, IV	[4], [5], [3], [1]
The efficacy of isolated limb perfusion (ILP) with melphalan is increased when combined with TNFα.	III-3	[1]

Evidence-based recommendation	Grade
It is recommended that isolated limb perfusion (ILP) be considered prior to amputation in patients with extremity sotf tissue sarcoma, particularly in the setting of metastatic disease.	**C**

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

Back to top

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?

Back to top

2.18.4 References

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Back to top

2.18.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.19 Treatment responses assessment

Contents

2.19.1 What are the measures to assess treatment response in BSST's?

2.19.1.1 Introduction

For some sarcomas, particularly osteosarcoma and the Primitive neuroectodermal tumors (PNET)/Ewing's family of tumours, histologic evidence of a substantial level of 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. In addition, given the large size of many bone and soft tissue sarcoma (STS), the possibility of achieving tumour shrinkage prior to surgical resection has obvious 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 preoperative setting. Courses of such preoperative 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 preoperative therapy and may even grow or spread in the interim, the delay potentially rendering the tumour unresectable. Monitoring of the tumour is required to assess the response to preoperative therapy and to tailor the approach in case of a suboptimal response.

2.19.1.2 What approaches are used to monitor response to preoperative therapy?

Two principal approaches have been used to monitor preoperative 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 pretreatment data to repeat measurement carried out at predefined intervals during the treatment phase. After resection, these preoperative changes are correlated with the degree of tumour necrosis as assessed by histopathological examination.

Back to top

2.19.1.3 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.[1] 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.[2][3] Similarly, in osteosarcomas increased signal intensity on MRI predicted poor response but the reverse did not hold for good response. However in the setting of preoperative radiation therapy for STS radiologic size increase was not predictive of poor response.[4]

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.[5] There is some evidence that the adapted Choi criteria, using a combination of reduced tumor size and decreased density on contrast-enhanced CT, are more predictive of response in soft tissue sarcomas, particularly for Gastrointestinal stromal tumours (GISTS).[6]

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 OS and the Ewing family of tumours.[7][8] However the specific SUV indices used and the timing of the PET scan after the start of therapy are widely variable. 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.[9] Furthermore, PET provides whole body imaging, useful for detecting occult metastases in the lungs, bones and viscera.

Scintigraphy using 99mTc-MIBI,[10] or 201Tl[11] 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.[12][13]

Back to top

2.19.1.4 Other

In a small series genomic alterations in tumour samples pre and post NAC have been correlated with likelihood of response to chemotherapy.[14] 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.[15]

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 NAC.[16]

Back to top

2.19.2 Evidence summary and recommendations

Evidence summary Functional imaging such as FDG PET imaging, often in combination with volumetric approaches (CT or MRI) can be used in assessing response to preoperative therapy in bone and soft tissue sarcomas. **Level IV**

Evidence-based recommendation	Grade
It is recommended to include response monitoring systems in the surveillance of bone and soft tissue sarcoma patients undergoing preoperative chemotherapy or radiation therapy and to standardise this process.	**D**

Back to top

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Back to top

2.19.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.20 Follow-up

Contents

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 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.

Back to top

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 BSST. Choice of CT/MRI will be guided by site (e.g. extremity versus retroperitoneum).

Back to top

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 and MRI can be useful modalities, but the cost-efficacy of these modalities has not been evaluated. There is no established role in long-term surveillance for functional imaging (eg. PET) which should be reserved for selected patients as a problem solving tool, rather than a primary diagnostic/surveillance tool.

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.

Back to top

2.20.1.4 Metastatic recurrence

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

Surgical metastastectomy is the only potential salvage procedure for pulmonary sarcoma metastases. 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 ($p<0.05$).[10]

Serial monitoring with chest CT could give rise to early detection of pulmonary metastases, chance for metastastasectomy and eventually survival advantage[10] athough interpretation of data would be thwarted by possible lead-time bias.

Pulmonary metastasectomy offers three year overall survival between 30-42%.[11]

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.

Back to top

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 BSST by providing greater opportunities for adequate re-operation or salvage therapy.	III-3	[6], [5], [4]

Evidence-based recommendation	Grade
In patients undergoing surveillance for local recurrence,regular clinical examination is recommended.	**D**

Practice point
Routine cross sectional imaging could 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.

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	[10]

Evidence-based recommendation	Grade
High risk patients in whom pulmonary metastasectomy would be considered to undergo three to six month CT chest until five years. Low dose protocol non contrast CT chest is the modality of choice for pulmonary surveillance. In patients not considered suitable for pulmonary metastasectomy, chest X-ray alone may be appropriate	**D**

Practice point

Follow-up intervals recommended in current multinational guidelines are each three months in years one and two after diagnosis, every two to four months in years three and four, every six months in years five to ten and every six to twelve months thereafter. Each visit should include a history and physical examination and a chest X-ray/CT chest.

Late metastases may occur >10 years after diagnosis and there is no universally accepted stopping point for tumor surveillance.

For patients enrolled in clinical trials, the above recommendations may vary in accordance with the follow-up protocols of these trials.

Back to top

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?

Back to top

2.20.4 References

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Back to top

2.20.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

2.21 Guideline development process

2.21.1 Guideline development process

2.21.1.1 Introduction

Cancer Council Australia (CCA) was approached by the Australasian Sarcoma Study Group to develop Clinical Practice Guidelines for the Management of 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 guideline development process, conducting the literature searches, appraising the literature and formulating and grading recommendations, followed the guideline development process outlined below.

Back to top

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

Back to top

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:

2.21.1.3.1 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 to referral to a specialist centre in bone and soft tissue tumours?
- What defines high-risk populations for bone and soft tissue tumours?

2.21.1.3.2 Multidisciplinary Treatment

- What is the role of prognostic algorithms 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?

2.21.1.3.3 Chemotherapy (systemic therapies)

- What is the role for adjuvant systemic therapy in BSTT?
- What is the role for systemic therapy in advanced BSTT?

2.21.1.3.4 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, 3D CRT, brachytherapy, extra-corporeal radiotherapy and proton therapy in the management of BSTTs?

2.21.1.3.5 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?

2.21.1.3.6 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?

Back to top

2.21.1.4 Develop a search strategy

Appropriate search strategies were constructed for each clinical question. MeSH terms were agreed by the Working Party members and where 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.

Back to top

2.21.1.5 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.

Back to top

2.21.1.6 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
	A randomised	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among	A prospective	A	A randomised

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
II	controlled trial	consecutive patients with a defined clinical presentation	cohort study	prospective cohort study	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 ■ 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	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ■ Historical control study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
	■ Interrupted time series without a parallel control group				■ 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.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Back to top

2.21.1.7 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
	population/s studied in body	population/s	population/s studied in body of evidence differ	population/s studied in body of evidence

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
Generalisability	of evidence are the same as the target population for the guideline	studied in the body of evidence are similar to the target population for the guideline	to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	different to target population and hard to judge whether it is sensible to generalise to target population
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)

Back to top

2.21.1.8 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

Back to top

2.21.1.9 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.

Back to top

2.21.1.10 Public consultation

The guidelines was released for public consultation to all interested parties in Australia for the period from 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 groups and sponsors via link to the site. All feedback on the draft received during the consultation period in Australia was reviewed by the Guidelines Working Party topic authors. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence.

Back to top

2.21.2 References

<references>

Back to top

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2.22 Working party members

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2.23 Conflict of interest register

Competing interest declarations

Working party member	Competing interest declaration
Assoc Prof Chris Hemmings	No competing interest to declare.
Associate Professor Gelareh Farshid	No competing interest to declare.
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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.

Working party member	Competing interest declaration
Dr Fiona Bonar	No competing interest to declare.
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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.
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.
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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.

Working party member	Competing interest declaration
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

Cell A	Cell B
Cell C	Cell D