London and South East Sarcoma Network
Patient Management Policy

This document has been compiled by members of the London and South East Sarcoma Network (LSESN) and approved by all consultants. It is reviewed and updated regularly. The purpose of the Policy is to define standards of care for patients with sarcoma and to guide patient management. It should be seen as a reference document and not as a substitute for multidisciplinary team discussion and decision-making in the management of individual patients.

Introduction

This document is intended as a guide to the management of sarcoma patients being treated within the University College Hospital (UCH) and Royal Marsden Hospital (RMH) Sarcoma Units, linked treating centres participating in multidisciplinary team (MDT) discussions (Southampton University Hospital), and centres delivering treatments by designated practitioners. Surgery is carried out at RMH and the Royal National Orthopaedic Hospital (RNOH). Both units have their own unit-specific guidelines, which give a greater level of detail. The document should also be considered in conjunction with the most recent version of the LSESN Sarcoma Advisory Group Chemotherapy Guidelines, the LSESN Follow-up Guidelines (http://lsesn.nhs.uk/guidelines.html) and national guidelines from the British Sarcoma Group (available at http://www.britishsarcomagroup.org.uk/treating-sarcoma/guidelines/2147483647/).

Sarcoma patients may present in a variety of ways. A multidisciplinary approach is pursued for all the cases in the two Units. All new patients will be presented and discussed at the MDT meeting, and a management plan decided based on the policies contained below. After the MDT discussion the patient will be provided with contact details for a key worker during working hours and who to contact for emergencies out of hours.

Both Sarcoma Units run broad portfolios of clinical trials. All patients will be considered for appropriate clinical studies, and referrals may be made between units for studies not open at both.

Disclaimer

1 Soft tissue sarcoma

There are multiple histological subtypes of soft tissue sarcoma (STS), but these are usually grouped under the heading of STS for the purpose of treatment. Some specific histological subtypes are identified where management is distinct and different. National guidelines for the management of soft tissue sarcoma have been published by the British Sarcoma Group (http://www.britishsarcomagroup.org.uk/treating-sarcoma/guidelines/), which can be considered in conjunction with this policy.

1.1. Diagnosis and staging

1.1.1. Soft tissue sarcomas at all sites

- MRI and/or CT scan of primary site
- CT chest to assess for pulmonary metastases (chest X-ray may suffice in some circumstances, e.g. elderly patients)
- CT or MRI abdomen and pelvis if myxoid liposarcoma
- Preoperative biopsy

1.1.2. Retroperitoneal STS

In contrast to extremity STS, core biopsy may be avoided if radiological appearances are felt to be diagnostic.

1.2. Treatment of localised disease

1.2.1. Surgery

1.2.1.1. Extremity STS

Surgery is the chief treatment modality in the case of localised, resectable sarcoma. All new cases of soft tissue sarcoma must be discussed in the MDT for consideration of surgery. The aim of surgery is complete excision with negative margins. Positive margins require re-excision if feasible.

1.2.1.2. Retroperitoneal STS

The main treatment modality is surgery. For low grade liposarcoma, local recurrence is compatible with extended survival, but patients may require multiple further palliative laparotomies. The phase III STRASS trial, which assessed the role of pre-operative radiotherapy in retroperitoneal sarcoma, closed in 2017, and results are awaited. Until this trial reports, there is still uncertainty as to the role or pre-operative radiotherapy in retroperitoneal sarcomas. Pre-operative radiotherapy may be considered on an individual patient basis for intermediate/high grade tumours (e.g. liposarcoma, pleomorphic sarcoma) when margins are anticipated to be close, and radiotherapy can be technically delivered. Radiotherapy in this context would usually be intensity-modulated radiotherapy.

1.2.1.3. Primary thoracic/chest wall sarcomas

Patients with potentially operable thoracic disease will have surgery at the Royal Brompton Hospital (RBH), and should be discussed in the weekly video-conferenced Sarcoma Thoracic MDT shared between RBH, RMH, and UCH.

1.2.2. Radiotherapy

Detailed radiotherapy guidelines for the management of all soft tissue sarcomas including target volume definitions and dose fractionation are specified in the current individual Unit radiotherapy guidelines. Radiotherapy may be delivered conventionally, or with intensity modulated radiotherapy (IMRT) where indicated. Some patients may be eligible for treatment with proton beam therapy (PBT) as part of the NHS overseas programme, including patients with tumours in difficult locations that may benefit from the specific dosimetric features of PBT in sparing normal tissues enabling optimal radiotherapy delivery, for example para-spinal soft tissue tumours. Reference should be made to current eligibility criteria (https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b01/).

1.2.2.1. Pre-operative radiotherapy

Pre-operative radiotherapy can be considered in all cases where radiotherapy is judged to be definitely required as part of management of the primary tumour. It should be particularly considered for patients with myxoid liposarcoma, which is recognised to be particularly radiosensitive. There will be circumstances where pre-operative radiotherapy may not be the best option:

- When the indication for radiotherapy is not clear, e.g. small tumours, low grade tumours
- When a definite diagnosis has not been possible pre-operatively
- Rapidly growing and/or painful symptomatic tumours
- Patient is unwell with systemic systems due to tumour (weight loss, fever, anaemia)
- Presence of distant metastatic disease

1.2.2.2. Post-operative radiotherapy

Decisions on post-operative radiotherapy are made on an individual patient basis following MDT discussion of the resection pathology. Post-operative radiotherapy is considered for tumours that are:

- High grade Trojani 2 or 3
- ≥ 5 cm in size
- Deep to the deep fascia
- Close margins
- R1 margins (if re-excision is not possible)
- Trojani grade 1 tumours, in sites difficult to salvage surgically, if relapse occurs.

1.2.3. Adjuvant Chemotherapy

Adjuvant chemotherapy is not associated with definite evidence of improved overall survival, but meta-analysis data have shown a significant improvement in local tumour control and relapse-free survival with the use of doxorubicin–based chemotherapy.

Adjuvant chemotherapy is not given routinely, but can be considered for patients with chemo-sensitive subtypes (e.g. synovial sarcoma) those with particularly high-risk tumours, e.g. pleomorphic rhabdomyosarcoma; malignant peripheral nerve sheath (Triton) tumours; angiosarcomas (including breast); head and neck sarcomas; extra-skeletal osteosarcoma. The standard regimen is doxorubicin and ifosfamide.

1.2.4. Fertility

Male patients receiving chemotherapy, or radiotherapy to tumours in proximity to the testes, are offered sperm banking. Female patients may be referred for oocyte

harvesting where funding allows, and there is sufficient time before treatment needs to start.

Pre-menopausal female patients receiving radiotherapy to the pelvis may be considered for oophoropexy/ovarian transposition in order to try to preserve fertility.

1.3. Treatment of advanced (inoperable) or metastatic disease

1.3.1. Palliative chemotherapy/systemic therapy for advanced disease

- First-line chemotherapy:
  - Single agent doxorubicin
  - Doxorubicin and olaratumab
  - Combination doxorubicin and ifosfamide chemotherapy can be considered in the following situations:
    - Fit patients up to approximately 60 years of age, in view of superior progression free survival, following discussion with patient
    - Rapidly progressing disease,
    - When a rapid disease response is clinically important
- Liposomal doxorubicin (Caelyx) may be used in place of doxorubicin for patients with cardiac impairment (*funding via Cancer Drugs Fund*)
- Combination doxorubicin and ifosfamide may also be used for specific indications, including rapidly progressive disease, or when the increased response rate of combination chemotherapy is desirable.
- Second-line chemotherapy is usually single agent ifosfamide (standard 3 day schedule, or prolonged low dose 14-day infusion). This may also be used as first-line therapy if cardiac function is impaired.
- Third-line chemotherapy options include:
  - Trabectedin
  - Gemcitabine ± docetaxel
  - Pazopanib (*no NHS funding at present*)
  - Dacarbazine ± gemcitabine
  - Oral cyclophosphamide ± prednisolone
- All patients will be considered for appropriate clinical trials open at each unit.

Additional specific systemic therapy options may be considered for certain histological subtypes.

1.3.1.1. <u>Angiosarcoma:</u>

- First-line chemotherapy options:
  - Single agent doxorubicin ± olaratumab/ifosfamide.
  - Paclitaxel (particularly in elderly patients)
- Second-line chemotherapy options include:
  - Paclitaxel.
  - Liposomal doxorubicin (Caelyx), especially for skin angiosarcomas (e.g. face and scalp), or radiation-induced, usually chest wall following radiotherapy for breast cancer (*no NHS funding at present*)
- Propranolol – in combination with other treatments. Propranolol has been designated by the EMA with orphan status on 12.12.16, on the basis that the sponsor provided 'sufficient information to show that propranolol might be of significant benefit for patients with angiosarcoma, because early studies show

improved progression-free survival when the medicine was used in combination with standard treatments'.

1.3.1.2. Leiomyosarcoma:

- First-line chemotherapy: Doxorubicin ± olaratumab/ifosfamide
- Second line chemotherapy options include:
  - Ifosfamide may be considered, although there is retrospective evidence that ifosfamide-containing regimens may be inferior to doxorubicin alone [2].
  - Trabectedin
  - Gemcitabine ± docetaxel
  - Dacarbazine ± gemcitabine

1.3.1.3. Myxoid liposarcoma:

  - First-line chemotherapy: Doxorubicin ± olaratumab/ifosfamide.
  - Trabectedin has shown particular activity in this subtype and may be considered as second/third line therapy in preference to other agents.
  - Third line chemotherapy:
    - Eribulin *(no NHS funding at present)*

1.3.1.4. Cardiac/pulmonary vessel sarcoma:

- Due to the risk of cardiotoxicity (if radiotherapy is to be administered following chemotherapy), liposomal doxorubicin can be used instead of conventional doxorubicin (*no NHS funding at present*).

1.3.1.5. Well/de-differentiated liposarcoma:

- First-line chemotherapy: Doxorubicin ± olaratumab.
- Second-line chemotherapy: Ifosfamide (standard 3 day schedule, or prolonged low dose 14-day infusion).
- Third line chemotherapy:
  - Trabectedin
  - Eribulin (*no NHS funding at present*)

1.3.1.6. Alveolar soft part sarcoma:

- Considered to be chemo-resistant, such that conventional chemotherapy is not used.
- Cedirinib (compassionate use program via drug company)
- Consider for clinical trials of new agents.

1.3.1.7. Extraskeletal myxoid chondrosarcoma:

- Considered to be chemo-resistant, such that conventional chemotherapy is not used.
- Consider for clinical trials of new agents.

1.3.1.8. Dermatofibrosarcoma protruberans:

- Consider use of imatinib for locally advanced inoperable disease (*funding via Individual Funding Request application*)

1.3.1.9. Inflammatory myofibroblastic tumour:

- Consider corticosteroids.
- Check ALK status, consider crizotinib for ALK positive tumours (*funding via Individual Funding Request application*)

- Consider for clinical trials of new agents.

1.3.2. Locally ablative therapies

Patients with small volume metastatic disease that are not amenable to surgery, or who wish to avoid surgery, or who are not fit for surgery, can be considered for locally ablative therapies including:

- Microwave radio-frequency ablation
- Cryotherapy
- Embolisation (liver metastases)
- Stereotactic ablative radiotherapy (SABR)

1.3.3. Surgery

Selected patients with oligo-metastatic disease may be suitable for surgical resection, if clinically appropriate. Decisions are made on an individual patient basis, following discussion at MDT. The most likely indication is resection of lung metastases. Patients are discussed in the weekly Thoracic Sarcoma MDT (video-conferenced between Royal Brompton Hospital, RMH and UCH).

1.3.4. Palliative radiotherapy

Patients can be treated with radiotherapy to palliate locally advanced or metastatic disease, or to consolidate disease response after palliative chemotherapy. Fractionation is decided on an individual patient basis.

1.3.5. Follow-up of soft tissue sarcoma

There are no published data to indicate the optimal routine follow-up policy. Relapses are most likely to occur to the lungs. Follow-up therefore focuses on surveillance of the primary site and the lungs.

- Clinical examination
- Chest x-ray
- Other investigations as clinically indicated
- Recommended intervals for follow-up:
    - Every 3 months for years 1 - 2.
    - Every 6 months for years 3 - 5.
    - Annually thereafter, discharging from clinic at 10 years

For the most up-to-date schedule, see current LSESN Follow-up Guidelines (http://lsesn.nhs.uk/guidelines.html).

2. Gastrointestinal Stromal Tumour (GIST)

2.1. Diagnosis and staging

- CT/MRI of primary site
- Chest & abdominal (liver and pelvis) imaging
- Pathology review
- Gene mutation analysis (patients with resected localised disease at intermediate or high risk of recurrence; all patients with locally advanced/metastatic disease)

2.2. Treatment of localised disease

- Standard treatment of localized GIST is complete surgical excision.

- If resection is R1 → re-excision should be considered.
- If tumour rupture occurs, a spillage of tumour cells into the peritoneal cavity must be assumed, indicating occult metastatic peritoneal disease. These patients are considered as being metastatic and should be considered for life-long imatinib.
- In potentially operable cases, with high surgical morbidity → consider neo-adjuvant imatinib.

2.3. Adjuvant medical therapy

Adjuvant imatinib is licensed by the EMA for 'adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment'. Adjuvant imatinib is currently given for 3 years' duration. 'Significant risk' is left to the interpretation of individual clinicians. In LSESN, adjuvant imatinib is offered to patients at high risk of relapse (≥50% risk according to Miettinen and Lasota, 2006). NHS funding is via the Cancer Drugs Fund.

Adjuvant imatinib can be considered in patients with KIT exon 11 mutations. However, it is not routinely recommended in the following situations:

- KIT exon 9 mutation (poorer outcomes with adjuvant treatment than KIT exon 11 patients)
- KIT exon 13, 17 mutations (uncertain efficacy)
- PDGFRA exon 18 D842V mutations (imatinib resistant)
- KIT, PDGFRA wild type (uncertain efficacy)
- BRAF mutations (uncertain efficacy)
- SDHB expression loss (uncertain efficacy)

2.4. Treatment of advanced disease

2.4.1. Medical therapy for advanced disease

- First-line treatment:
  - Imatinib 400 mg OD
  - Patients with a KIT exon 9 mutation should be treated with imatinib 800mg OD (no *NHS funding at present*).

  Patients with the resistant PDGFRA exon 18 D842V mutation are expected not to respond to imatinib, sunitinib or regorafenib, and so should be considered for local therapies where possible, or clinical trials.
- Second line treatment:
  - Imatinib 800mg OD (no *NHS funding at present*).
  - Sunitinib
- Third line treatment:
  - Regorafenib

2.4.2. Surgery

Surgery may be considered in selected patients following discussion at MDT:

- To resect residual disease. This is best performed at maximal response to systemic therapy.
- To resect a single site of disease progression.
- Surgery for generalised disease progression is not of benefit and is not recommended.

2.4.3. Radiofrequency ablation

Radiofrequency ablation can be considered to treat liver metastases, as a less invasive alternative to surgical resection. RFA is best performed at maximal response to systemic therapy, or to treat a single site of disease progression.

2.4.4. Radiotherapy

Radiotherapy, including SABR, can be considered in selected patients for palliation, if the site of disease is encompassable within radiotherapy treatment fields.

2.4.5. Disease response evaluation

- CT is the standard imaging modality to assess response to systemic therapy, using change in tumour size and tumour density.
- MRI may be preferred for specific sites such as rectum
- FDG–PET scan has proved to be highly sensitive in early assessment of tumour response, but is not recommended for routine ongoing assessment of disease response. However, it may be helpful to clarify specific clinical problems, for example when surgery is being considered, or for patients on 2nd or 3rd line therapies, when disease response assessment is recognised to be more difficult.

2.4.6. Follow-up

There are no published data on the optimal schedule for follow-up. Both units follow the follow-up schedule defined in the current LSESN Follow-up Guidelines (http://lsesn.nhs.uk/guidelines.html).

3. Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is typically a cancer of childhood, and is rare in adults. It may affect the extremities, genitourinary system, head and neck region, trunk, or other less frequent sites.

1.1.1 Four main variants are recognised:

- Embryonal rhabdomyosarcoma (including botryoid variant)
- Alveolar rhabdomyosarcoma
- Spindle cell rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma (occurs in adults, is treated as a high grade soft tissue sarcoma)

3.1. Diagnosis and staging:

- Biopsy, pathology review
- CT/MRI of primary site
- CT chest, abdomen and pelvis
- Whole body bone scan or PET-CT scan
- Bilateral bone marrow aspirate and trephine
- Assessment of cerebrospinal fluid for parameningeal tumours.
- Routine bloods including LDH and alkaline phosphatase.

3.2. Treatment of localised disease

Patients are stratified according to the risk of their disease, based on a number of prognostic factors. The principles of treatment are:

- Low Risk → surgery + chemotherapy.

- Standard Risk → surgery + chemotherapy ± radiotherapy.
- High Risk → chemotherapy + surgery + radiotherapy.
- Very High Risk → chemotherapy +/- surgery + radiotherapy.

Local therapy (surgery and/or radiotherapy) is carried out at around week 13. Vincristine, actinomycin D, and ifosfamide are the main chemotherapy agents.

Detailed guidelines for the management of all rhabdomyosarcomas including risk classification and available clinical trials are specified in the current Unit guidelines.

3.3. Treatment of metastatic disease

Patients are treated as follows:

- IVADo x 4 → IVA x 5 → vinorelbine/cyclophosphamide x 12 cycles
- Local treatment remains important, and if possible should be surgical resection of the primary site, with radiotherapy to local and all metastatic sites where possible. Local treatment will be around cycles 7 – 9.

3.4. Treatment of relapsed disease

Treatment will be given on an individualised basis, and will depend on whether or not the primary therapy contained doxorubicin. Patients should be considered for clinical trials if available. Regimens that can be considered (as recommended by the current EpSSG 2005 protocol) include:

3.4.1. Previous doxorubicin

- Irinotecan and vincristine has shown to have activity in relapsed rhabdomyosarcoma (Mascarenhas et al, JCO, 2010)

- Vinorelbine and cyclophosphamide

3.4.2. No previous doxorubicin

- Topotecan, vincristine, doxorubicin

3.5. Follow-up of rhabdomyosarcoma

- Clinical evaluation of the primary site
- MRI or CT scan of the primary site as clinically indicated
- Chest x-ray

Recommended intervals for follow-up:

- Every 2 months in the first year.
- Every 3 months in years 2 - 3.
- Every 6 months in years 4 - 5.
- Annually thereafter.

For the most up-to-date schedule, see current LSESN Follow-up Guidelines (http://lsesn.nhs.uk/guidelines.html).

4. Bone sarcomas

All localised bone sarcomas are treated at the RNOH and UCH. Soft tissue extra-skeletal Ewing's sarcomas are also treated at RMH. Surgery for thoracic bone sarcomas is carried out at the Royal Brompton Hospital. All cases of suspected bone tumour should be discussed at MDT. After an appropriate imaging assessment, pre-treatment biopsy of bone sarcomas should be carried out at RNOH. Any external histopathology of bone sarcomas should be reviewed at RNOH prior to treatment.

4.1. Osteosarcoma

4.1.1. Diagnosis and staging

- Biopsy
- Plain x-rays of primary site
- MRI of primary site ± CT
- CT chest
- Whole-body bone scan *or* PET-CT *or* whole body MRI
- Routine blood tests, including ALP and LDH.

4.1.2. Treatment of localised disease

Neo-adjuvant chemotherapy (10 weeks) → local therapy (surgery if at all possible) → post-operative adjuvant chemotherapy (18 weeks). The chemotherapy regimen is MAP (doxorubicin, cisplatin, methotrexate). This may be modified to AP alone (without methotrexate) for patients >40 years.

Surgery is carried out after a 10-week block of induction chemotherapy. The aim will be to carry out limb salvage, but amputation may be required if limb salvage cannot achieve complete excision. In specific patient groups (e.g. pelvic craniofacial), all chemotherapy may be given prior to surgery, acknowledging the difficulty of giving further chemotherapy after major surgery. For these patients, PET-CT may be helpful to aid assessing response to treatment during chemotherapy. Histological response to induction chemotherapy is assessed on the resection specimen as >90% necrosis (good response) or <90% necrosis (poor response). However, at present there is no evidence to support changing chemotherapy regimen if the histological response is poor.

Radiotherapy is not routinely used in osteosarcoma, and is believed not to be an adequate substitute for surgery. However, radiotherapy may be used if surgery is not possible. The most common tumour site for which radical radiotherapy is used as local therapy is the pelvis. Intensity-modulated radiotherapy (IMRT) may offer the opportunity to deliver higher radiation doses, which may improve the chances of achieving local tumour control. Proton radiotherapy may also be considered for inoperable pelvic or spinal tumours. Cases should be submitted to the UK Proton Panel for consideration for funding, to be treated abroad. Reference should be made to current eligibility criteria (https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b01/).

Radiotherapy may be considered postoperatively after limb-salvage surgery. Decisions are made after MDT discussion on an individual patient basis, but factors that may be taken into consideration include:

- Poor response to chemotherapy (<90% tumour necrosis)
- Close margins infiltrative into soft tissue
- Positive margins when no further surgery is possible

- Pathological fracture through the primary tumour

4.1.3. Treatment of primary metastatic disease

4.1.3.1. Primary resectable metastatic osteosarcoma

Patients with metastatic disease that is surgically resectable (usually limited lung metastases) should be treated with curative intent following the same principals of non-metastatic osteosarcoma.

4.1.3.2. Primary widely metastatic osteosarcoma

Patients with widely metastatic disease at presentation will not be curable. Chemotherapy will be given with palliative intent, and will be MAP or AP, decided on an individual patient basis. Local therapy should be considered, to achieve local control. Depending on individual circumstances, other regimens active in osteosarcoma, especially ifosfamide-containing, may be considered if toxicity of (M)AP is to be avoided.

4.1.3.3. Pulmonary metastatectomy

Patients with limited isolated lung metastases, should be considered for pulmonary metastatectomy. These cases should be discussed in the Thoracic Sarcoma MDT. Surgery should be timed during the block of consolidation adjuvant chemotherapy, following resection of the primary tumour.

4.1.4. Treatment of recurrent disease

Recurrence may be local or distant. Local recurrences are treated surgically. The role of further chemotherapy is not clear, and is decided on an individual patient basis. Distant recurrences are most commonly in the lungs, but can more rarely occur at other sites. Patients with isolated lung metastases may still be curative, if the disease is surgically resectable.

- Second line chemotherapy:
  - Ifosfamide and etoposide
- Third line chemotherapy:
  - Gemcitabine and docetaxel
  - Consider for clinical trials
- Radiotherapy can be used for palliation.

4.1.5. Follow-up of Osteosarcoma

Follow-up of osteosarcoma patients should include:

- Physical examination of the primary site of the disease.
- Assessment of the function and possible complications of any reconstruction/prosthesis.
- Local x-rays and chest x-ray
- Other investigations as clinically indicated
- Recommended intervals for follow-up:
  - Every 2 months for year 1.
  - Every 3 months for years 2-3.
  - Every 6 months for years 4-5.
  - Annually thereafter.

For the most up-to-date schedule, see current LSESN Follow-up Guidelines (http://lsesn.nhs.uk/guidelines.html).

4.2. Ewing's sarcoma

4.2.1. Diagnosis and staging

- Biopsy
- Plain x-rays of primary site
- MRI (or CT) of primary site
- CT chest
- Whole-body bone scan *or* whole body MRI *or* PET-CT
- Bilateral bone marrow biopsy aspirate and trephine (can be omitted if PET scan is negative)
- Routine blood tests, including LDH

4.2.2. Treatment of localised disease

Neo-adjuvant chemotherapy → local therapy (surgery and/or radiotherapy) → adjuvant chemotherapy. Local therapy will be discussed at the local MDT, and also in the National Ewing's Sarcoma MDT.

4.2.2.1. Primary chemotherapy

Multidrug chemotherapy for Ewing's sarcoma includes vincristine (V), doxorubicin (D), ifosfamide (I), etoposide (E), cyclophosphamide (C) and actinomycin-D (A). Current treatment protocols used are:

- VIDE x 6 → VAI x 8 *or* VAC x 8
- VDC/IE x 14 cycles (as per COG AEWS0031 study protocol experimental arm)
- Enrolment and treatment in Euro-Ewing-2012 study protocol

Patients with localised disease and poor histological response following induction chemotherapy and surgery should considered for high dose chemotherapy and peripheral blood stem cell transplant.

4.2.2.2. Surgery

Wide excision of the primary tumour is performed after 14 - 18 weeks of induction chemotherapy. It is important that local therapy is not delayed, as this can result in poorer treatment outcomes. Histological response is assessed on the resection specimen as >90% necrosis (good response) or <90% necrosis (poor response).

4.2.2.3. Radiotherapy

- Acceptable alternative to surgery if radical excision is not possible, or is considered too morbid, e.g. sacral tumours.
- Post-operative radiotherapy may be required. Decisions will be made on an individual patient basis, following discussion at MDT. *Relative* indications are:
    - Close surgical margins
    - Positive surgical margins and further surgery not possible
    - Poor response to chemotherapy (<90% necrosis)
- Pre-operative radiotherapy may be considered if surgery will be difficult, and radiotherapy could improve the chances of a complete excision.
- Chemotherapy can be given concurrently with radiotherapy. It may be necessary to omit doxorubicin or actinomycin-D depending on treatment site, as these will potentiate the acute radiotherapy reaction. Omission should be from 3 weeks before staring to 3 weeks after completing radiotherapy.
- Patients requiring radical radiotherapy involving the spinal cord or larger volumes of bowel must not receive busulphan as part of high dose chemotherapy regimen.

- Some patients may benefit from PBT, for example:
  - Patients aged 24 years or younger
  - Patients with pelvic or spinal tumours where proton beam radiotherapy may offer a dosimetric advantage over standard photon radiotherapy in delivering the optimal radiotherapy dose

  Reference should be made to current eligibility criteria (https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b01/).

For details of radiotherapy techniques and doses, see individual unit guidelines.

4.2.3. Treatment of primary metastatic disease

Patients with metastatic disease may be still potentially curable, depending on the volume and distribution of metastases. Therefore, the same treatment approach is used as for patients with localised disease.

4.2.3.1. Chemotherapy

The same chemotherapy regimens are used as for patients with localised disease. There is no evidence for using high dose chemotherapy with peripheral blood stem cell rescue outside of a clinical trial.

4.2.3.2. Local therapy for the primary tumour

The primary tumour may be resected, if this can be achieved with acceptable morbidity In some clinical situations, radiotherapy may be considered as an alternative as definitive local therapy, particularly for patients with more widely metastatic disease believed to be incurable. Decisions on local therapy for such patients are decided on an individual patient basis. For details of radiotherapy, see section 4.2.2.3.

4.2.4. Treatment of recurrent disease

This will depend on sites of metastases, and timing of relapse. Patients who have relapsed more than two years from completing primary treatment, with small volume (usually lung only) metastases, may still be potentially curable, and could be considered for induction chemotherapy (e.g. ifosfamide +/- etoposide), and high dose chemotherapy (busulphan and melphalan) with peripheral blood stem cell rescue depending on disease response.
Patients not falling into this selected group would be considered incurable, and are treated with palliative intent.

4.2.4.1. Palliative chemotherapy regimens

- Ifosfamide +/- etoposide
- Cyclophosphamide and topotecan
- Irinotecan and temozolomide
- Gemcitabine and docetaxel
- Consider entry into suitable clinical trials.

4.2.4.2. Palliative radiotherapy

Palliative radiotherapy may be helpful, with dose and technique dependent on clinical situation.

4.2.5. Follow-up of Ewing's Sarcoma

- Physical examination of the primary site of the disease

- Assessment of the function and possible complications of any reconstruction.
- Plain films of prosthesis and chest x-ray
- Other investigations as clinically indicated
- Recommended intervals for follow-up are:
    - Every 2 months for the year 1.
    - Every 3 months for years 2 - 3.
    - Every 6 months for years 4 - 5.
    - Thereafter annually.

For the most up-to-date schedule, see current LSESN Follow-up Guidelines (http://lsesn.nhs.uk/guidelines.html).

4.3. Other Bone Sarcomas

4.3.1. Chondrosarcoma

Chondrosarcoma is one of the most frequently occurring bone sarcomas of adulthood. Most chondrosarcomas arise as primary malignant tumours, and the majority are low grade. Histological subtypes include:

- Central (primary and secondary)
- Peripheral
- Dedifferentiated
- Mesenchymal
- Clear cell

4.3.1.1. Diagnosis and staging

- Biopsy
- Plain x-rays of primary site
- MRI (or CT) of primary site
- CT chest
- Whole-body bone scan

4.3.1.2. Treatment of localised disease

Treatment of localised disease is almost exclusively surgical, aiming for complete excision of the tumour. Adjuvant radiotherapy is not indicated after complete excision with wide margins. Post-operative PBT may be considered by marginal/intralesional excisions of spine, pelvic and base of skull tumours, if further surgery is not possible. Chemotherapy with doxorubicin, cisplatin +/- methotrexate may be used in the neo-adjuvant or adjuvant setting for de-differentiated chondrosarcoma. Mesenchymal chondrosarcoma is more chemo-sensitive than other types of chondrosarcoma, and neoadjuvant/adjuvant chemotherapy is recommended which is usually doxorubicin and ifosfamide-based.

4.3.1.3. Treatment of locally advanced/metastatic disease

Inoperable, locally advanced and metastatic chondrosarcoma has a poor prognosis because of resistance to conventional treatments. Radical radiotherapy may be used to treat inoperable locally advanced tumours, as high dose palliation. Palliative radiotherapy may be used for all types of chondrosarcoma. Grade 1 – 3 chondrosarcoma is acknowledged to be chemo-resistant, such that there is no role for chemotherapy for metastatic disease. Patients should be considered for appropriate clinical trial protocols. Metastatic dedifferentiated chondrosarcoma is treated as for osteosarcoma, although it is less chemosensitive. Surgery should be

considered for operable metastatic disease, particularly pulmonary metastatic disease, on an individual patient basis.

4.3.2. Chordoma

Chordomas are rare bone tumours, originating from remnants of the notochord. They typically arise in the sacrum (50–60% of cases), skull base region (25–35% of cases), and cervical and thoracolumbar vertebrae (15% of cases). Chordomas are usually low-grade tumours, with distant metastases seen infrequently at initial diagnosis. "Dedifferentiated" chordoma is seen in ~5% of cases.

4.3.2.1. Treatment of localised disease

The mainstay of treatment is complete local excision. Even with clear margins, local recurrence rates can be high, and post-operative radiotherapy should be considered, aiming to deliver doses of at least 70Gy. To achieve this, consider use of IMRT, or proton beam radiotherapy via application to the UK Proton Panel for approval and funding (https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b01/).

4.3.2.2. Treatment of inoperable locally advanced disease

Treat with radical radiotherapy aiming to achieve local tumour control, IMRT will be required to achieve adequate doses which should aim to be at least 70Gy. At present, inoperable chordoma is not an approved indication for proton beam radiotherapy overseas.

4.3.2.3. Treatment of progressing locally advanced/metastatic disease

Surgery should be considered where possible. Chordoma is acknowledged to be chemo-resistant, such that there is no role for chemotherapy for metastatic disease, except for dedifferentiated chordoma, when doxorubicin and cisplatin chemotherapy may be considered, although evidence for its use is limited. Systemic therapy using targeted agents such as imatinib first line, and sorafenib (requiring IFR) as second line treatment may be considered. Patients should be considered for appropriate clinical trial protocols.

4.3.3. Giant cell tumour

Giant cell tumour of bone is a benign condition (although rarely, it can occur in a malignant form).

4.3.3.1. Diagnosis and staging

- Primary presentation
  - Biopsy
  - Plain x-rays of primary site
  - MRI (or CT) of primary site
  - CT chest not done (incidence of lung metastases at diagnosis 0.006%)
  - Chest x-ray for patients presenting with pathological fracture – high risk group with high levels of circulating tumour DNA
- Recurrent disease
  - Consider re-biopsy to exclude malignant change, if clinical suspicion
  - Plain x-rays of primary site
  - MRI (or CT) of primary site
  - CT chest (17% risk of lung metastases after local recurrent)

- Treatment of localised disease

It is treated by surgery, either curettage or excision with reconstruction depending on site and extent. For locally advanced tumours, embolization, or down-staging with denosumab (a RANK ligand inhibitor) may be helpful prior to surgery. Radiotherapy may also be considered as local therapy when other options have been exhausted, as local control rates are high.

- Treatment of recurrent/metastatic disease

Patients should be considered for surgery whenever possible. For inoperable metastatic disease, treatment options are limited. There is recent evidence for activity of denosumab, which according to the licence may be used in patients whose disease cannot be treated by surgery or in whom surgery would cause severe problems.

• Special sites

○ *Gynaecological sarcomas*

Cases will frequently be identified within the gynaecological oncology MDT, often as an unexpected diagnosis following surgery. All cases will also be discussed within the Sarcoma MDT.

▪ Uterine leiomyosarcoma

- Diagnosis and staging

- Pathology review, including ER and PR status
- MRI/CT of abdomen and pelvis
- CT thorax

- Treatment of localised disease

- Surgery – total abdominal hysterectomy. Bilateral salpingoophorectomy may be avoided in pre-menopausal women. No indication for routine pelvic lymphadenectomy.
- Adjuvant chemotherapy is not routinely recommended
- Adjuvant pelvic radiotherapy is not indicated for early stage (FIGO I/II) disease
- Consider pelvic radiotherapy in selected high risk patients (FIGO III/IVA)

- Treatment of metastatic/recurrent disease

Chemotherapy

- First-line chemotherapy is single agent doxorubicin.
- Second-line chemotherapy options include:
  - Trabectedin
  - Gemcitabine ± docetaxel
  - Gemcitabine ± dacarbazine
  - Dacarbazine
- Hormone-antagonist therapies may be considered for tumours that express oestrogen receptors (ER) and/or progesterone receptors (PgR), including:
  - Progestogens (megesterol acetate, medroxyprogesterone acetate)
  - Aromatase inhibitors after oophophorectomy (anastrazole, letrozole, exemestane)

- Combination doxorubicin and ifosfamide may be used for specific limited indications, including rapidly progressive disease, or when the increased response rate of combination chemotherapy is desirable.
- All patients will be considered for appropriate clinical trials open at each unit.

5.1.1.2.1. Radiotherapy

Patients can be treated with radiotherapy to palliate locally advanced or metastatic disease. Fractionation is decided on an individual patient basis

5.1.1.2.2. Surgery

Selected patients with metastatic disease may be suitable for surgical resection, if clinically appropriate. Decisions are made on an individual patient basis, following discussion at MDT. The most likely indication is resection of lung metastases. Patients are discussed in the Thoracic Sarcoma MDT (video-conferenced between Royal Brompton Hospital, RMH and UCH on Monday afternoon).

▪ Endometrial stromal sarcoma

• Diagnosis and staging

- Pathology review, including ER and PR status
- MRI/CT of abdomen and pelvis
- CT thorax

• Treatment of localised disease

- Surgery – total abdominal hysterectomy and bilateral salpingoophorectomy. Bilateral salpingoophorectomy is usually routinely recommended in view of the hormonal responsiveness of this tumour, but may be avoided in selected young pre-menopausal women wishing to avoid an early menopause. No indication for routine pelvic lymphadenectomy.
- Adjuvant pelvic radiotherapy is not indicated for early stage (FIGO I/II) disease.
- Consider pelvic radiotherapy in selected high risk patients (FIGO III/IVA).
- Adjuvant hormone-antagonist therapy (aromatase inhibitor) for 2 years may be considered in selected high-risk patients, although evidence to support this is limited.

• Treatment of metastatic disease

Surgery

Endometrial stromal sarcoma is an indolent disease with potentially a very long natural history. It is therefore appropriate to consider surgical resection of metastatic disease, on a selected individual patient basis.

Hormone-antagonist therapies

Hormone-antagonist therapies may be used to treat and palliate metastatic disease:

- Progestogens (megesterol acetate, medroxyprogesterone acetate)
- Aromatase inhibitors after oophophorectomy (anastrazole, letrozole, exemestane)

Chemotherapy

If hormone-antagonist options have been exhausted, palliative chemotherapy can be considered (see section 5.1.1.4.1).

- **Undifferentiated endometrial sarcoma**

  - Diagnosis and staging

- Pathology review, including ER and PR status
- MRI/CT of abdomen and pelvis
- CT thorax

  - Treatment of localised disease

- Undifferentiated endometrial sarcoma is an aggressive disease with high metastatic potential. A more intensive approach to treatment of early stage disease in young fit patients may therefore be considered.
- Surgery – total abdominal hysterectomy. Bilateral salpingoophorectomy may be avoided in pre-menopausal women. No indication for routine pelvic lymphadenectomy.
- Consider adjuvant doxorubicin and ifosfamide chemotherapy in young fit patients.
- Adjuvant pelvic radiotherapy may be considered following chemotherapy.

  - Treatment of metastatic/recurrent disease

Chemotherapy

- First-line chemotherapy is single agent doxorubicin ± olaratumab/ifosfamide.
- Second-line chemotherapy is single agent ifosfamide. This may also be used as first-line therapy if cardiac function is impaired.
- Third-line chemotherapy options include:
  - Trabectedin
  - Gemcitabine ± docetaxel
  - Dacarbazine ± gemcitabine
- All patients will be considered for appropriate clinical trials open at each unit.

Radiotherapy

Patients can be treated with radiotherapy to palliate locally advanced or metastatic disease. Fractionation is decided on an individual patient basis.

Surgery

Selected patients with metastatic disease may be suitable for surgical resection, if clinically appropriate. Decisions are made on an individual patient basis, following discussion at MDT. The most likely indication is resection of lung metastases. Patients are discussed in the Thoracic Sarcoma MDT (video-conferenced between Royal Brompton Hospital, RMH and UCH on Mondays afternoons).

Detailed guidelines for the management of uterine sarcomas are specified in current unit guidelines.

○ *Breast sarcomas*

Breast sarcomas are most likely to be diagnosed within the site-specific breast MDT. Breast sarcomas encompass:

- Radiation-associated sarcomas
- Non-radiation-associated sarcomas
- Sarcomas of the skin of the breast area
- Sarcomas from mammary glands
- Angiosarcoma
- Malignant phylloides tumours

- **Diagnosis and staging**

- Pathology review
- Mammograms/breast MRI
- CT thorax

- **Treatment of localised disease**

- Surgery (breast conserving surgery may be used, if sufficiently wide surgical margins can be achieved).
- Mastectomy (involving the muscular fascia) is generally preferred for larger tumours, and for angiosarcomas (which are diffuse and aggressive).
- Consider postoperative radiotherapy for non-radiation-associated tumours.
- May consider adjuvant doxorubicin and ifosfamide chemotherapy in high-risk patients (e.g. angiosarcoma; high grade radiation-associated sarcomas for whom radiotherapy cannot be used to achieve local control).
- For locally advanced tumours, neo-adjuvant chemotherapy may be considered.

- **Treatment of metastatic disease**

This is as for metastatic soft tissue sarcoma at other sites (see section 1.3.1) and angiosarcoma (see section 1.3.1.1).

○ *Head and neck sarcoma including skull base*

Head and neck sarcomas are likely to be diagnosed within the site-specific head and neck MDT. Patients will be managed by the sarcoma oncologist, in conjunction with the head and neck MDT for surgical management. Tumours may be of soft tissue (soft tissue sarcomas, rhabdomyosarcoma) or bone (Ewing's sarcoma, osteosarcoma, chondrosarcoma) origin.

- **Diagnosis and staging**

- Pathology review
- MRI and CT head and neck
- CT thorax
- Other staging (e.g. bone scan, bone marrow aspirate and trephine) as indicated.

- **Treatment of localised disease**

For rhabdomyosarcoma and bone sarcomas, see tumour-specific sections above. For other soft tissue sarcomas management is likely to include a combination of chemotherapy, radiotherapy and surgery, which reflects the difficulty in achieving local tumour control in this disease location. The exact ordering of treatment modalities will be determined on an individual patient basis, following MDT discussion.

- **Treatment of metastatic disease**

See tumour-specific sections above.

○ *Pigmented villonodular synovitis*

Pigmented villonodular synovitis (also named tenosynovial giant cell tumour of tendon sheath) is a benign condition involving synovium of joints, bursae and tendon sheaths. Tumours can be intra- or extra-articular, and localised or diffuse. Commonest sites include knee, ankle and hip joints. Very rarely, these tumours

can undergo malignant change. Presentation is usually as painless swelling of the joint, but as disease becomes more advanced with bony destruction, symptoms of pain, stiffness and loss of function may develop.

▪ Diagnosis and staging

- Imaging of the disease site with MRI
- Biopsy to confirm diagnosis

▪ Treatment

- Limited asymptomatic disease may be managed by observation
- For symptomatic disease, surgery may be considered, aiming to resected as much disease as possible, while trying to avoid morbid procedures
- For diffuse disease, complete excision may be difficult or impossible, and local recurrence rates can be high. In addition, surgery may not improve symptoms of pain and loss of function. Post-operative or definitive radiotherapy may therefore be considered to avoid further morbid surgery, and prevent further joint destruction and loss of function. Radiotherapy is give in moderate doses (36 – 50Gy) and is associated with high (>90%) local control rates
- For patients with locally advanced symptomatic disease for whom local therapies (surgery and radiotherapy) have been exhausted, consider treatment with imatinib, which has shown to be active in this disease, for improvement in symptoms and function.

○ *Fibromatosis*

Fibromatosis is a rare benign but locally aggressive condition, which can arise at any site, including:

- Abdominal wall
- Mesentery
- Other extra-abdominal locations, including limbs

The natural history is unpredictable (with the possibility of long-lasting stable disease and even occasional spontaneous regressions). Fibromatosis does not metastasise.

▪ Diagnosis and staging

- Pathology review and gene mutational analysis for beta-catenin
- Imaging of the disease site – CT for intra-abdominal disease, MRI for other soft tissue sites
- Appropriate evaluation in syndrome-associated cases, e.g. Gardner's syndrome, with colonoscopy.
- If tumour is negative for beta-catenin, baseline colonoscopy should be performed.

▪ Treatment

- Given the long and potentially unpredictable natural history of this disease, a period of observation may be the best initial option. Exceptions to this approach would be patients with potentially life-threatening extra-abdominal locations (e.g. head and neck region); and intra-abdominal fibromatosis.
- For cases with demonstrated disease progression, optimal treatment needs to be individualized following multidisciplinary discussion. Treatment options can include:
    - Surgery (without any adjuvant therapy)

- Radiotherapy (may be post-operative or definitive)
- Locally ablative therapies (microwave radiofrequency ablation, cryotherapy)
- Systemic therapies:
  - Endocrine therapies (tamoxifen, toremifene, GnRH analogues)
  - Non-steroidal anti-inflammatory drugs
  - Low-dose chemotherapy (e.g. methotrexate and vinblastine; oral vinorelbine)
  - Standard-dose chemotherapy (using pegylated liposomal doxorubicin (Caelyx – no NHS funding at present), and other regimens active in soft tissue sarcomas)

It is reasonable to employ the less toxic therapies before the more toxic ones in a stepwise fashion.