London and South East Sarcoma Network
Patient Management Policy

This document has been compiled by members of the London and South East Sarcoma Network and approved by all consultants. It will be reviewed and updated annually. 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 on the University College Hospital (UCH) and Royal Marsden Hospital (RMH) Sarcoma Units. Surgery is carried out at the Royal Marsden Hospital and the Royal National Orthopaedic Hospital (RNOH). Both Units have their own unit-specific guidelines which give a greater level of detail.

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 multidisciplinary team (MDT) meeting, and a management plan constructed based on the policies contained below. After the MDT discussion the patient will be provide 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 recently been published by the British Sarcoma Group [1], 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 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.

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 IMRT (intensity modulated radiotherapy) where indicated.

1.2.2.1. Pre-operative radiotherapy

Pre-operative radiotherapy can be considered in cases where tumours are of borderline operability, and radiotherapy may facilitate a complete excision. It should be particularly considered for patients with myxoid liposarcoma, which is recognised to be particularly radiosensitive.

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

1.3. Treatment of advanced (inoperable) disease

1.3.1. Palliative chemotherapy/systemic therapy for advanced disease

- First-line chemotherapy is single agent doxorubicin.
- Second-line chemotherapy is usually 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
  - Oral cyclophosphamide and prednisolone
- 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.

Specific systemic therapy options may be considered for certain histological subtypes.

1.3.1.1. Angiosarcoma:

- First-line chemotherapy is single agent doxorubicin.
- Second-line chemotherapy options include:
  - Paclitaxel.
  - Liposomal doxorubicin, especially for skin angiosarcomas (e.g. face and scalp), or radiation-induced, usually chest wall following radiotherapy for breast cancer.

1.3.1.2. Leiomyosarcoma:

- First-line chemotherapy: Doxorubicin
- Second line chemotherapy: Ifosfamide may be considered, although there is some evidence that ifosfamide-containing regimens may be inferior to doxorubicin alone [2].
- Third-line chemotherapy: Trabectedin or gemcitabine ± docetaxel.

1.3.1.3. Myxoid liposarcoma:

- First-line chemotherapy: Doxorubicin.
- Trabectedin has shown particular activity in this subtype as second/third line therapy.

1.3.1.4. Cardiac/pulmonary vessel sarcoma:

- Due to the risk of cardiotoxicity (as radiotherapy is administered following chemotherapy in the majority), liposomal doxorubicin can be used instead of conventional doxorubicin.

1.3.1.5. Well/de-differentiated liposarcoma and synovial sarcoma:

- First-line chemotherapy: Doxorubicin.
- Second-line chemotherapy: Ifosfamide (standard schedule, or prolonged infusion).

1.3.1.6. Alveolar soft part sarcoma:

- Considered to be chemo-resistant, such that conventional chemotherapy is not used.
- Consider for clinical trial.

1.3.1.7. Extraskeletal myxoid chondrosarcoma:

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

1.3.1.8. Dermatofibrosarcoma protruberans:

- Consider use of imatinib (acts via blocking of PDGFRβ receptor) for locally advanced inoperable disease.

1.3.1.9. Inflammatory myofibroblastic tumour:

- Consider corticosteroids.

1.3.2. Radiofrequency ablation

Patients with lung and liver metastases that are not amenable to surgery, or patients are not fit for surgery, can be considered for radio-frequency ablation (RFA).

1.3.3. 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 alternate Mondays and Wednesdays).

1.3.4. Palliative radiotherapy

Patients can be treated with radiotherapy to palliate locally advanced or metastatic disease. 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
- Baseline MRI of primary site 6 months after completing radiotherapy
- 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.

For the most up-to-date schedule, see current UCH/RNOH unit follow-up guidelines.

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 peritoneal disease.
    - In potentially operable cases, with high surgical morbidity → consider neoadjuvant imatinib.

2.3. Adjuvant medical therapy

Adjuvant imatinib is licensed by the EMA for use in patients at intermediate and high risk of relapse. Adjuvant imatinib following resection of localised GIST was considered by NICE in 2010, but was not approved. Therefore, use of adjuvant imatinib is not routine, but will be considered on an individual patient basis, and will require a funding application demonstrating exceptionality. If the decision is made to use adjuvant imatinib, the currently published clinical trial data support its use for 1 year [3]. Data presented in abstract form at ASCO 2011 have shown that 3 years of imatinib is superior to 1 year in patients with high risk tumours, both in terms of relapse free and overall survival, supporting the use for 3 years of adjuvant treatment in high risk patients [4].

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. This is not approved by NICE and will require an individual funding request (IFR) application.
- Second line treatment:
  - Imatinib 800mg OD. This is not approved by NICE and will require an IFR.
  - Sunitinib
- Third line treatment:
  - Consider for clinical trials

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 can be considered in selected patients for palliation, if the site of disease is encompassable within radiotherapy portals.

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, particularly 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 UK GIST Guidelines.

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.

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 phoshatase.

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.
For the very high risk patients doxorubicin may be added to the standard regimens.

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 with metastatic RMS may be entered into the BERNIE study (open at selected paediatric oncology centres, but not at the Sarcoma Units at RMH or UCH). Patients not entered into this study may be registered within EpSSG 2005 study, in an obervational arm:

- 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. Regimens that can be considered (as recommended by the current EpSSG 2005 protocol) include:

3.4.1. Previous doxorubicin

Recommended chemotherapy is the Topo-Carbo regimen. This is a 16-week schedule of topotecan, carboplatin, etoposide and cyclophosphamide (see EpSSG 2005 protocol).
A further option would be irinotecan and vincristine which has shown to have acitivity in relapsed rhabdomyosarcoma (Mascarenhas et al, JCO, 2010):

Irinotecan 50 mg/m^2 days 1 – 5 in a 3-weekly schedule
Vincristine 1.5mg/m^2 days 1 and 8 in a 3 weekly schedule.

N.B. A CCLG phase II study of irinotecan, vincristine +/- temezolamide is due to open in the near future.

3.4.2. No previous doxorubicin

Recommended chemotherapy is the Doxo-Carbo regimen. This is a 16-week schedule of doxorubicin, carboplatin and cyclophosphamide (see EpSSG 2005 protocol).

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 individual unit guidelines.

4. Bone sarcomas

All bone sarcomas are treated at the RNOH and UCH. Soft tissue extra-skeletal Ewing's sarcomas are also treated at RMH. All cases of suspected bone tumour should be discussed at MDT. After an appropriate imaging assessment, pre-treatment biopsy should be carried out at RNOH. Any external histopathology should be reviewed at RNOH prior to treatment. National guidelines for the management of bone sarcomas have recently been published by the British Sarcoma Group [5], which can be considered in conjunction with this policy.

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 (pelvic, and 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 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.

Radiotherapy may be considered postoperatively after limb-salvage surgery. Decisions are made at MDT on an individual patient basis, but *relative* indications include:

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

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 will be carried out, to achieve local control.

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 UCH/RNOH unit follow-up guidelines.

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
- 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-99 study protocol

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; these patients will only be treated within the Euro-Ewing-99 protocol on study).

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

4.2.3. Treatment of primary metastatic disease

Patients with metastatic disease are 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. Patients with metastatic disease beyond isolated lung metastases are not eligible for the Euro-Ewing-99 study. There is no evidence for using high dose chemotherapy with peripheral blood stem cell rescue outside of a clinical trial.

4.2.3.2. Surgery

The primary tumour should be resected. Surgical resection of residual metastases may be considered if of limited volume.

4.2.3.3. Radiotherapy

- Treatment of the primary site as for localised disease.
- Patients with pulmonary metastases not receiving high dose busulphan should be considered for whole lung irradiation.
- Patients requiring radical radiotherapy involving the spinal cord or larger volumes of bowel must not receive busulphan (as part of high dose chemotherapy regimen; these patients will only be treated within the Euro-Ewing-99 protocol on study).

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

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 (ifosfamide +/- etoposide), and high dose chemotherapy (busulphan and melphelan) 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
- 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 UCH/RNOH unit follow-up guidelines.

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. Chemotherapy with doxorubicin, cisplatin +/- methotrexate may be used in the neo-adjuvant or adjuvant setting for de-differentiated chondrosarcoma.

4.3.1.3. Treatment of locally advanced/metastatic disease

Inoperable, locally advanced and metastatic chondrosarcomas have 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 unusually. “Dedifferentiated” chordoma is observed 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 up to 70Gy. To achieve this, consider use of intensity-modulated radiotherapy (IMRT), or proton radiotherapy. There are at present no proton facilities in the UK, so patients must be referred to an overseas centre. Patients must be submitted to the UK Proton Panel for approval and funding, see:http://www.specialisedservices.nhs.uk/service/proton-beam-therapy.

4.3.2.2. Treatment of inoperable locally advanced disease

Treat with radical radiotherapy to achieve high dose palliation. It is likely that IMRT will be required to achieve adequate doses. At present, inoperable chordoma is not an approved indication for proton therapy overseas.

4.3.2.3. Treatment of 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. Patients should be considered for appropriate clinical trial protocols. There is some limited evidence for the use of targeted therapies in metastatic disease, including imatinib, sunitinib, and mTOR inhibitors. Use of these drugs requires IFR applications for funding.

4.3.3. Giant cell tumour

4.3.3.1. Treatment of localised disease

GCT is treated by surgery, either curettage or excision with reconstruction depending on site and extent.

4.3.3.2. Treatment of recurrent/metastatic disease

Surgery should be utilised where possible. For inoperable metastatic disease, treatment options are limited. There is recent evidence for activity of denosumab, a RANK ligand inhibitor. Patients may be treated within appropriate clinical trials, as this is an unlicensed indication.

5. Special sites

5.1. Gynaecological sarcomas

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

5.1.1. Uterine leiomyosarcoma

5.1.1.1. Diagnosis and staging

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

5.1.1.2. Treatment of localised disease

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

5.1.1.3. Treatment of metastatic/recurrent disease

Chemotherapy

- First-line chemotherapy is single agent doxorubicin.
- Second-line chemotherapy is usually single agent ifosfamide. This may also be used as first-line therapy if cardiac function is impaired.
- Third-line chemotherapy options include:
  - Trabectedin (licensed)
  - Gemcitabine ± docetaxel
  - Dacarbazine
- 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.

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 alternate Mondays and Wednesdays).

5.1.2. Endometrial stromal sarcoma

5.1.2.1. Diagnosis and staging

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

5.1.2.2. Treatment of localised disease

- Surgery – total abdominal hysterectomy and bilateral salpingoophorectomy. 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).
- Consider adjuvant hormonal treatment (aromatase inhibitor) for 2 years in selected high risk patients.

5.1.2.3. 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.

Hormonal therapy

Hormonal therapy with aromatase inhibitors or progestagens may be used to treat and palliate metastatic disease.

Chemotherapy

If hormonal therapeutic options have been exhausted, palliative chemotherapy can be considered (see section 5.1.1.4.1).

5.1.3. Undifferentiated endometrial sarcoma

5.1.3.1. Diagnosis and staging

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

5.1.3.2. 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.

5.1.3.3. Treatment of metastatic/recurrent disease

Chemotherapy

- First-line chemotherapy is single agent doxorubicin.
- 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 (licensed)
  - Gemcitabine ± docetaxel
  - Dacarbazine
- 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.

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 alternate Mondays and Wednesdays).

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

5.2. Breast sarcomas

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

- Radiation-induced sarcomas
- Non-radiation-induced sarcomas
- Sarcomas of the skin of the breast area
- Sarcomas from mammary glands

- Angiosarcoma
- Malignant phyllodes tumours

5.2.1. Diagnosis and staging

- Pathology review
- Mammograms/breast MRI
- CT thorax

5.2.2. 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-induced tumours.
- Consider adjuvant doxorubicin and ifosfamide chemotherapy in high risk patients (e.g. angiosarcoma; high grade radiation-induced sarcomas for whom radiotherapy cannot be used to achieve local control).
- For locally advanced tumours, chemotherapy may be given neo-adjuvantly.

5.2.3. Treatment of metastatic disease

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

5.3. Head and neck sarcoma

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.

5.3.1. Diagnosis and staging

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

5.3.2. 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.

5.3.3. Treatment of metastatic disease

See tumour-specific sections above.

5.4. 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.

5.4.1. Diagnosis and staging

- Pathology review
- 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.

5.4.2. 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)
    - Radiation therapy
    - Systemic therapies:
        - Hormonal therapies (tamoxifen, toremifene, GnRH analogues)
        - Non-steroidal anti-inflammatory drugs
        - Low-dose chemotherapy (e.g. methotrexate and vinblastine; methotrexate and vinorelbine)
        - Low-dose interferon
        - Molecular therapies: imatinib
        - Standard-dose chemotherapy (using pegylated liposomal doxorubicin, 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.

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