

# Sarcoma Expert Advisory Group (SAG) Clinical Guidelines 2017

## Document Information

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## **1 Introduction and terms of reference**

The aim of this document is to draw together guidance for the referral and treatment of patients with bone and soft tissue tumours including sarcomas within the Northern England Strategic Clinical Network and referred to the North of England Bone and Soft Tissue Tumour Service from outside the Network area.

This guideline does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of individual patients. This is a reference document and not a substitute for multidisciplinary team (MDT) discussion. The guidelines will not cover all clinical situations in all patients, but where unusual circumstances exist, it is expected that management would be discussed in the appropriate site-specific MDTs.

These guidelines take into account NICE clinical guidelines and guidelines from other networks, in particular the London and South East Sarcoma Network (LSESN) as well as guidance from the British Sarcoma Group. It is recognised that these guidelines may change after adoption of new national service guidelines which are in development.

The guidelines should be reviewed on an annual basis. New treatments may be added as an addendum between revisions. However, readers should recognise that changes in practice may have occurred since these guidelines were approved.

## **2 General principles of sarcoma care**

Within the Northern England Strategic Clinical Network, the majority of patients with sarcoma receive all of their treatment within Newcastle Upon Tyne Hospitals, but some treatments are delivered in other centres in the network by agreement. For example, some chemotherapy and radiotherapy treatments are delivered at James Cook University Hospital, Middlesbrough. Sarcomas present in a wide range of anatomical sites and therefore some care may be delivered by agreement with an appropriate site-specific MDT. Each unit has its own treatment policies and procedures.

Sarcoma patients may present in a variety of ways. All new patients with sarcoma within the network should be discussed at the Bone and Soft Tissue Tumour multidisciplinary team (Sarcoma MDT) meeting, unless there is previous agreement about treatment (eg some superficial dermal sarcomas, and some GISTs) and a management plan constructed considering the guidelines that follow.

### **2.1.1 Pathology**

The diagnosis of sarcoma and other bone and soft tissue tumours can be difficult. All biopsies leading to a confirmed or suspected diagnosis of sarcoma should be reviewed by a specialist sarcoma pathologist (SSP). An SSP is one who regularly reports soft tissue and bone tumours and these form a significant component of their workload. He or she should successfully participate in the bone and soft tissue pathology EQA scheme, and be part of a properly constituted sarcoma MDT.

Pathology reports should include all the information required by the Royal College of Pathologists' histopathology dataset for soft tissue sarcomas, the dataset for primary bone tumours or the dataset for gastrointestinal stromal tumours. They should use the World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone (2013) and the Trojani grading system where appropriate.

All small cell sarcomas and some other tumours should have molecular/cytogenetic testing.

## **3 Clinical trials, audit and research**

All patients should be considered for appropriate clinical trials, and referrals may be made between units if patients wish to participate in a study open elsewhere.

All patients should be considered for tumour tissue banking in the Newcastle Biobank or as part of a clinical trial.

Data collection for audit should be supported by all clinicians in the service.

## 4 Lipomatous tumours

Lipomatous tumours commonly trigger referral to the Sarcoma MDT and efficient management is important, as is rapid reassurance and discharge of patients who do not have cancer and do not need further treatment. Some patients with confirmed malignant tumours containing fat require management appropriate for a soft tissue sarcoma. Management guidelines are as follows:

### 4.1 Superficial lipomatous tumours:

- Confirm with USS
- If deep or >7cm then investigate with MRI
- Removal of superficial lipomatous tumours can be considered if enlarging, >5cm or symptomatic. These can often be treated closer to home by the referring team.
- Otherwise can be discharged with advice to return if changes
- After resection, superficial lipomas and atypical lipomas do not need follow up. Discharge with advice.

### 4.2 Deep lipomatous tumours in the extremity:

- Confirm with MRI.
- If bland, homogenous discuss removal with patient. Considerations include size, symptoms, patient fitness and the potential difficulty of removal. There is a risk of dedifferentiation which may be higher with tumours >10cm and patients over 50 years of age. Overall risk is said to be <2%. Removal is by complete but close /planned marginal excision.
- If not homogenous consider image guided biopsy
- The role of PET scanning is not defined
- If dedifferentiated liposarcoma treat as soft tissue sarcoma
- After treatment patients with lipomas can be discharged with advice
- Patients with atypical lipomatous tumours are at risk of local recurrence, particularly if removal has been associated with capsular disruption or the dissection of critical anatomic structures from within the tumour, so follow up options should be discussed with patients.

### 4.3 Deep lipomatous tumours in high risk sites

- High risk sites include the retroperitoneum, mediastinum, spermatic cord and testis
- These are more likely to be atypical or low grade liposarcomas
- There is a higher risk of dedifferentiation of tumours in these sites
- Consider complete excision with negative margins
- Follow up for local recurrence of greater importance than in the extremity as local recurrence can lead to death, therefore consider regular local site imaging (eg CT abdomen).

## **5 Soft tissue sarcoma**

There are many histological subtypes of soft tissue sarcoma (STS), but these are usually grouped together for treatment. Some specific histological types are managed differently. The following applies principally to “adult type” soft tissue sarcomas. Soft tissue sarcomas in the skin are considered separately. Childhood Rhabdomyosarcoma will be discussed and reviewed in the Paediatric Oncology MDT and will be reviewed through the bone and soft tissue tumour service as appropriate. National guidelines for the management of soft tissue sarcoma have been published by the British Sarcoma Group <sup>1</sup>.

### **5.1 Diagnosis and staging**

#### **5.1.1 Soft tissue sarcomas at all sites**

- Patients with a suspected soft tissue sarcoma should be referred to the bone and soft tissue tumour service for biopsy and management before treatment.
- Some patients are referred after unplanned excision of a lump thought to be benign. This complicates further management and should be avoided if possible.
- Preoperative biopsy is usual before resection of a sarcoma.
- Small (<5cm), superficial tumours may be considered for excision biopsy if the predicted surgical field is straightforward to reexcise after confirmation of a sarcoma diagnosis.
- In the North of England Bone and Soft Tissue Tumour Service, biopsy is performed using a trucut needle under ultrasound guidance in most cases
- The direction of the biopsy needle and the insertion point should be carefully planned with a view to excision of the biopsy track during definitive surgery
- Once a diagnosis of sarcoma is established local staging is performed with MRI and/or CT scan of primary site if it has not already been performed
- CT chest is required to detect pulmonary metastases (chest X-ray may suffice in some circumstances, e.g. frail or unfit patients for whom treatment for metastases only detectable on CT would not be appropriate)
- CT chest, abdomen and pelvis if myxoid liposarcoma or lower extremity tumour with a propensity for lymph node involvement
- PET has some limited usefulness in staging, particularly when staging is critical to determine local treatment (eg when considering amputation).

#### **5.1.2 Retroperitoneal STS**

In contrast to extremity STS, preoperative core biopsy may be avoided if radiological appearances are felt to be diagnostic. However, the risk of implantation with core needles passed through a trocar is small.

## **5.2 Treatment of localised disease**

### **5.2.1 Surgery**

#### **5.2.1.1 Extremity and trunk STS**

Surgery is the chief treatment modality for localised, resectable sarcoma. All new cases of soft tissue sarcoma must be discussed in the Sarcoma MDT for consideration of surgery. The aim of surgery is complete excision with negative margins. Positive margins require surgical re-excision if feasible. Surgery should be performed by surgeons with expertise in the resection and reconstruction of soft tissue sarcoma, when appropriate in conjunction with surgeons with site or age-specific expertise.

#### ***Retroperitoneal STS***

The main treatment modality is complete surgical removal. For low grade liposarcoma, local recurrence is compatible with extended survival, but patients may require multiple further palliative laparotomies.

#### ***Primary thoracic/chest wall sarcomas***

Patients with potentially operable thoracic disease or tumours involving the chest wall will be discussed at the Sarcoma MDT and managed by the designated thoracic surgeons with other members of the MDT as required (eg plastic and/or orthopaedic surgeons).

### **5.2.2 Radiotherapy**

Detailed radiotherapy guidelines for the management of all soft tissue sarcomas including target volume definitions and dose fractionation are specified in the unit radiotherapy guidelines. There is a subset of soft tissue sarcomas that do not need radiotherapy if wide excision can be achieved. Radiotherapy may be delivered conventionally, or with intensity modulated radiotherapy (IMRT) where indicated.

#### **5.2.2.1 Pre-operative radiotherapy**

Pre-operative radiotherapy should be considered in certain situations where the size of the radiation field required and the dose for post-operative treatment are likely to be associated with significant late morbidity, or when the tumour is of borderline operability and pre-operative radiotherapy is judged to be capable of rendering the tumour operable. For certain radiosensitive histological subtypes, such as myxoid liposarcoma, pre-operative radiotherapy should be strongly considered given the degree of tumour shrinkage that can be achieved. Considerations include the risks of surgery and wound complications in a previously irradiated field.

#### **5.2.2.2 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)
- $\geq 5$  cm in single maximum dimension
- Deep to or involving 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

### **5.2.2.3 Adjuvant Chemotherapy**

Adjuvant chemotherapy is not associated with definite evidence of improved overall survival in soft tissue sarcoma, but meta-analysis data suggested an 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. Patients with relatively chemosensitive histological types may also benefit (eg synovial sarcoma in the extremity). The standard regimen is doxorubicin and ifosfamide.

### **5.2.2.4 Fertility**

Male patients receiving chemotherapy, or radiotherapy to tumours in proximity to the testes, should be offered sperm banking. Pre-menopausal female patients receiving radiotherapy to the pelvis may be considered for oophoropexy in order to try to preserve fertility.

## **5.3 Treatment of advanced (inoperable) disease**

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  $\pm$  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

## **5.4 Type-specific systemic therapy options**

### **5.4.1 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).

#### **5.4.2 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
- Third-line chemotherapy: Trabectedin or gemcitabine ± docetaxel.

#### **5.4.3 Myxoid liposarcoma**

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

#### **5.4.4 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.

#### **5.4.5 Well/de-differentiated liposarcoma and synovial sarcoma**

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

#### **5.4.6 Alveolar soft part sarcoma**

Considered to be chemo-resistant, such that conventional chemotherapy is not used.

- Consider for clinical trial.

#### **5.4.7 Extraskelatal myxoid chondrosarcoma:**

Considered to be chemo-resistant, such that conventional chemotherapy is not used.

- Consider for clinical trial.

#### **5.4.8 Dermatofibrosarcoma protruberans:**

- Consider use of imatinib (acts via blocking of PDGFR $\beta$  receptor) for locally advanced inoperable disease.

#### **5.4.9 Inflammatory myofibroblastic tumour:**

Consider corticosteroids. Consider entry into ALK inhibitor trial.

### **5.5 Metastatectomy**

Selected patients with surgically resectable metastatic disease (usually in the lung) may be considered for surgery, if clinically appropriate. Decisions are made on an individual patient basis, following discussion at MDT. Referral to the SABR MDT may be appropriate. Radiofrequency ablation may have a role in the treatment of metastases, particularly in liver or lung.

## 5.6 Palliative radiotherapy

Radiotherapy may be considered to palliate locally advanced or metastatic disease. Fractionation is decided on an individual patient basis.

## 5.7 Follow-up after treatment for soft tissue sarcoma

There are no published data to indicate the optimal routine follow-up regimen. Relapses are most likely to occur to the lungs. Follow-up therefore focuses on surveillance of the primary site and the lungs, but should also consider other aspects of survivorship, including disability, pain, lymphoedema and psychosocial support.

- Clinical examination
- Chest x-ray for patients who have had high grade tumours (Trojani grade 2 or 3) at each follow-up visit (see suggested follow-up intervals). For those with low grade tumours consider CXR every 6-12 months.
- Baseline MRI of primary site within 6 months after completing radiotherapy. In situations where the area is easily followed by physical examination further imaging might not be required.
- Recommended late radiation morbidity assessments and documentation at each clinical oncology follow up visit
- An assessment of physical functioning is recommended, ideally with the Toronto Extremity Salvage Score (TESS) outcome measure.
- Consider completion of the patient perceived change of status measure at each review.
- Other investigations as clinically indicated
- Recommended intervals for follow-up of high grade tumours:
  - Every 3 months for years 1 - 2.
  - Every 6 months for years 3 – 5
  - Annually thereafter to 8 or 10 years
- Recommended intervals for follow-up of low grade tumours: 6 monthly for 5 years then annually up to 10 years.

## 6 Gastrointestinal Stromal Tumour (GIST)

The key reference document is the British Sarcoma Group guidance, which will be updated in 2017 <sup>2</sup>. All patients with metastatic disease and all those with high grade tumours should be discussed at the Sarcoma MDT. Others including those with intermediate and low-risk GISTs (such as small tumours in the stomach under the care of the upper GI MDT) can be managed according to the protocol below and do not need to be routinely discussed by the Sarcoma MDT unless there are treatment uncertainties.

Other than in very exceptional circumstances, medical therapy will not be offered to patients with a working diagnosis of GIST without a tissue biopsy.

### 6.1 Diagnosis and staging

- CT/MRI of primary site

- Chest & abdominal (liver and pelvis) imaging
- EUS with or without biopsy may be used to evaluate tumours
- Pathology review
- Gene mutation analysis (patients with resected localised disease at intermediate or high risk of recurrence; all patients with locally advanced/metastatic disease)

### **6.1.1 Treatment of localised disease**

- Standard treatment of localized GIST is complete surgical excision. However, some smaller (<2cm) lesions can be observed.
- Tumours larger than 2cm can be managed conservatively if:
  - Homogenous appearance on CT scan, EUS or both.
  - Asymptomatic (GI bleed usually the commonest significant symptom).
  - Demonstration of minimal or no growth on serial imaging or serial endoscopy.
- Tumours greater than 4-5 cms are usually considered for surgery, provided the patient is fit enough and the risk-benefit balance is appropriate.
- If resection is R1, re-excision should be considered.
- If tumour rupture occurs, 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.

#### **6.1.1.1 Adjuvant medical therapy**

Adjuvant imatinib is licensed by the EMA for use in patients at intermediate and high risk of relapse. NICE TA326 (Nov 2014) supersedes the 2010 guidance recommending adjuvant Imatinib 400 mg OD for up to 3 years in patients with a high risk of recurrence, based on the Miettinen criteria (2006).

### **6.1.2 Treatment of advanced disease**

#### **6.1.2.1 Medical therapy for advanced disease**

First-line treatment:

- Imatinib 400 mg OD

Second line treatment:

- Imatinib 800mg OD. This is not approved by NICE and will require an IFR.
- Sunitinib

Third line treatment:

- Regorafenib is available through the Cancer Drugs Fund
- Consider for clinical trials

#### **6.1.2.2 Surgery for advanced disease**

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.

### 6.1.2.3 Radiofrequency ablation

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

### 6.1.2.4 Radiotherapy

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

### 6.1.2.5 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.

### 6.1.2.6 Follow-up

There are no published data on the optimal schedule for follow-up. However the follow-up schedule defined in the current UK GIST Guidelines is recommended.

Table from 2010 consensus guidelines:

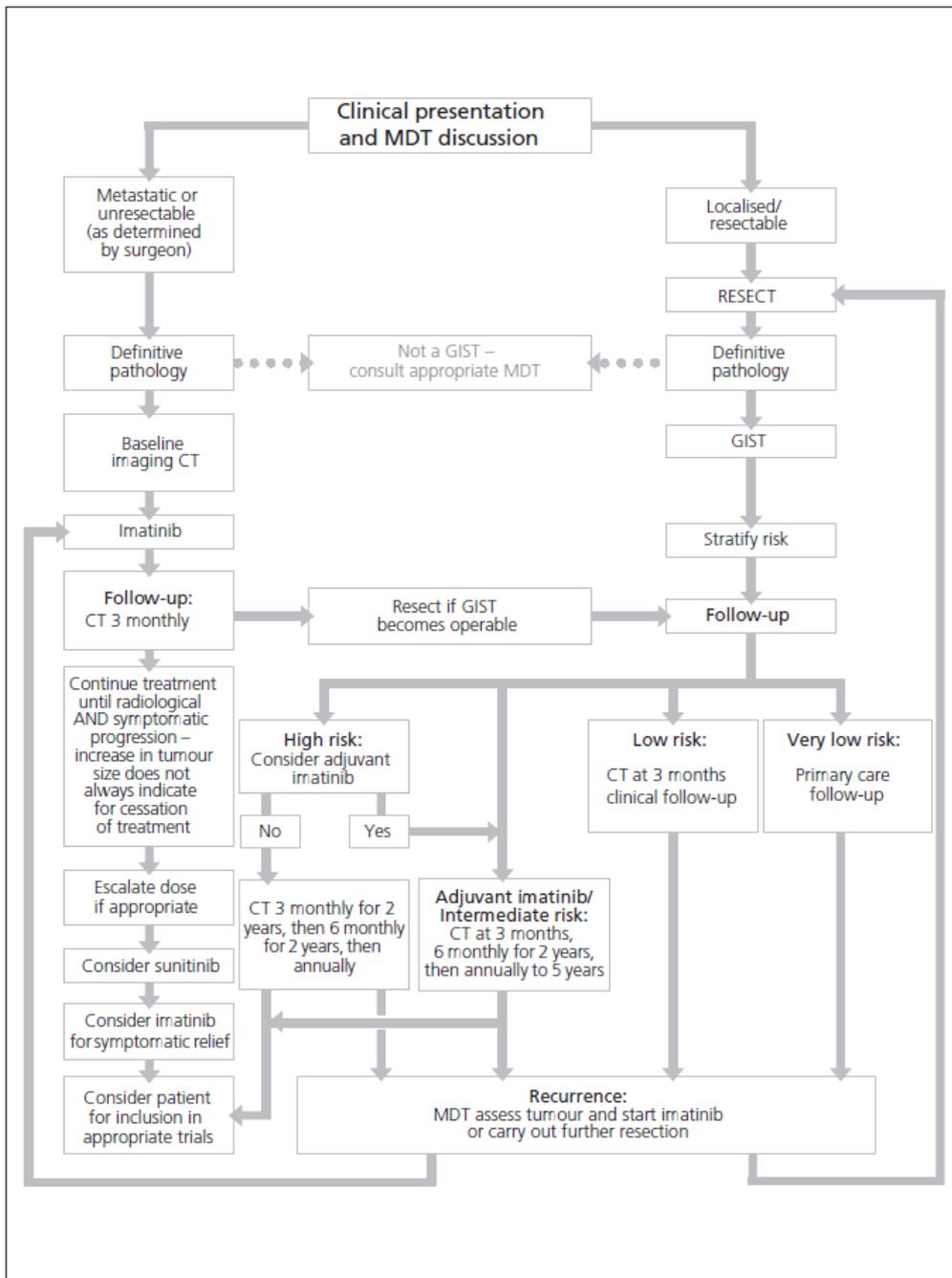
Table 4a: Risk of relapse (adapted from Miettinen and Lasota)<sup>74</sup>

Size cm	M/50HPF*	Gastric	Jejunal/Ileal	Duodenal	Rectal
≤2	≤5	Very Low (0%)	Very Low (0%)	Very Low (0%)	Very Low (0%)
>2≤5	≤5	Very Low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
>5≤10	≤5	Low (3.6%)	Moderate (24%)	-	-
>10	≤5	Moderate (12%)	High (52%)	High (34%)	High (57%)
≤2	>5	Very Low (0%)	High (50%)	-	High (54%)
>2≤5	>5	Moderate (16%)	High (73%)	High (50%)	High (52%)
>5≤10	>5	High (55%)	High (85%)	-	-
>10	>5	High (86%)	High (90%)	High (86%)	High (71%)

\*Mitotic count per 50 high power fields

*NB. According to more recent guidelines including the RCPATH minimum dataset for GISTs, the mitotic count per 5 square mm should be used instead of 50HPF.*

Algorithm of overall care



*NB. Some lesions may be treated by observation only as described in the text.*

## 7 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)

### 7.1 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.

### 7.2 Treatment of localised disease

Patients are stratified according to the risk of their disease, based on a number of prognostic factors. Paediatric patients should be treated in line with the now closed EpSSG RMS 2005 study which offers stratified treatment according to histology, stage and site.

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

### 7.3 Treatment of metastatic disease

Patients should be treated in line with the now closed EpSSG 2005 study:

- 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.

### 7.4 Treatment of relapsed disease

Treatment will be given on an individualised basis, and will depend on whether or not the primary therapy contained doxorubicin. Paediatric patients with recurrent disease should be considered for entry into the VIT study. Otherwise guidance on treatment is available in the EpSSG 2005 protocol.

## 7.5 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.

## 8 Bone sarcomas

All cases of suspected bone tumour should be discussed at the Sarcoma MDT. After an appropriate imaging assessment, pre-treatment biopsy should be carried out under the supervision of a bone sarcoma surgeon. Any external histopathology should be reviewed in the Sarcoma MDT prior to treatment. National guidelines for the management of bone sarcomas have been published by the British Sarcoma Group<sup>3</sup> which complements this guideline.

### 8.1 Osteosarcoma

There is no first line chemotherapy study open for patients with osteosarcoma at the present time.

#### 8.1.1 Diagnosis and staging

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

#### 8.1.2 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 of age. Mifurmatide is NICE approved for patients without metastatic disease and should be considered<sup>4</sup>.

Surgery is carried out after a 10-week block of induction chemotherapy. The usual aim is to carry out limb salvage, but amputation may be required if limb salvage cannot achieve complete excision. In specific patient groups (eg 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 not thought to be an adequate substitute for surgery. However, radiotherapy may be used if surgery is not possible, for example in the pelvis and sacrum. 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. Appropriate cases should be submitted to the UK Proton Panel to consider funding for treatment abroad or in the UK as proton beam therapy becomes available.

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

### **8.1.3 Treatment of primary metastatic disease**

#### **8.1.3.1 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.

#### **8.1.3.2 Primary widely metastatic osteosarcoma**

Patients with widely metastatic disease at presentation will not usually be curable. Chemotherapy will be given with palliative intent, and will be MAP or AP, decided on an individual patient basis. Local therapy for local control is usually appropriate.

#### **8.1.3.3 Pulmonary metastatectomy**

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

### **8.1.4 Treatment of recurrent disease**

Recurrence may be local or distant. Local recurrences are treated surgically if feasible. The role of further chemotherapy is not clear, and is decided on an individual patient basis. Distant recurrences most commonly occur in the lungs, but more rarely occur at other sites. Patients with isolated lung metastases may still be cured if the disease is surgically resectable. Patients without the potential for surgical cure aged <25 may be considered for entry into the lenvatinib (Eisai HOPE) study.

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

### **8.1.5 Follow-up after 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

## **8.2 Ewing's sarcoma**

At the present time, most patients would be considered for entry in to the EuroEwing 2012 study.

### **8.2.1 Diagnosis and staging**

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

### **8.2.2 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 MDT.

### **8.2.3 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

### **8.2.4 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 but volume change can make quantifying the degree of necrosis difficult. The aim of surgery should be to resect all of the anatomical structures involved in the original tumour volume before chemotherapy where possible.

### **8.2.5 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 (incomplete 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 starting to 3 weeks after completing radiotherapy.
- Patients requiring radical radiotherapy involving the spinal cord or larger volumes of bowel must not receive busulphan.

### **8.2.6 Treatment of primary metastatic disease**

Patients with metastatic disease are still potentially curable, depending on the volume and distribution of metastases. Patients with bone metastases unfortunately have a poorer prognosis than those with lung metastases. Therefore, the same treatment approach is used as for patients with localised disease.

#### **8.2.6.1 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.

#### **8.2.6.2 Surgery**

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

#### **8.2.6.3 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

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

### **8.2.7 Treatment of recurrent disease**

This will depend on sites of metastases, and timing of relapse. Patients should be considered for the rEECur study. 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 melphalan) with peripheral blood stem cell rescue depending on disease response.

Patients not falling into this select group would be considered incurable, and are treated with palliative intent.

### **8.2.7.1 Palliative chemotherapy regimens**

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

### **8.2.7.2 Palliative radiotherapy**

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

### **8.2.8 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.

## **8.3 Other Bone Sarcomas**

### **8.3.1 Chondrosarcoma**

Chondrosarcoma is one of the most frequently occurring bone sarcomas of adulthood. Most chondrosarcomas arise as primary malignant tumours (albeit in pre-existing lesions such as enchondromata), and the majority are low grade.

Histological subtypes include:

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

#### **8.3.1.1 Diagnosis and staging**

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

#### **8.3.1.2 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 considered in the neo-adjuvant or adjuvant setting for de-differentiated chondrosarcoma.

### **8.3.1.3 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.

### **8.3.2 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.

#### **8.3.2.1 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 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>).

#### **8.3.2.2 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.

#### **8.3.2.3 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.

### **8.3.3 Giant cell tumour of bone**

#### **8.3.3.1 Treatment of localised disease**

Giant cell tumour of bone (GCT) is primarily treated by surgery, either by curettage or excision with reconstruction depending on site and extent. There is an evolving role for denosumab, a RANK ligand antibody to improve local control in high-risk or unresectable disease. Risks of denosumab include osteonecrosis of the mandible and rebound hypercalcaemia <sup>5</sup>.

### **8.3.3.2 Treatment of recurrent/metastatic disease**

Surgery is the most appropriate treatment where possible. For inoperable metastatic disease, treatment options are limited, but may include denosumab. Radiotherapy is indicated only for rare cases of unresectable, residual or recurrent GCTB in which denosumab is contraindicated or unavailable and when surgery would lead to unacceptable morbidity.

## **9 Special sites**

### **9.1 Gynaecological sarcomas**

#### **9.1.1 Background**

- Sarcomas presenting to gynaecological MDTs are rare - approximately 280 new cases of gynaecological sarcomas are diagnosed annually compared with approximately 18,000 carcinomas of gynaecological origin.
- Some guidelines are available from other countries <sup>6</sup>.
- There is some evidence that survival for uterine sarcoma may be lower in the UK than other countries.
- The biology and clinical behaviour of the main types of gynaecological sarcoma differ markedly from tumours of epithelial origin and most gynaecological cancer MDTs do not have specific expertise in gynaecological sarcoma.
- Sarcomas are mainly uterine but can also rarely arise from the cervix, ovary, fallopian tube, vagina and vulva.
- The commonest sarcomas are leiomyosarcomas (low and high grade). Other diagnoses include endometrial stromal sarcoma, undifferentiated uterine sarcomas, rhabdomyosarcomas and perivascular epithelioid (mesenchymal) cell tumours (PEComas).
- Carcinosarcomas and adenosarcomas are outside this guideline unless sarcoma is the predominant histological component of a tumour.
- About two-thirds of gynaecological sarcomas are not diagnosed pre-operatively but discovered on histopathology after hysterectomy carried out for presumed fibroids or other benign conditions.
- Imaging features which are atypical for fibroids, particularly in older patients, should raise the suspicion of sarcoma and prompt liaison with the identified sarcoma specialists responsible for gynaecological sarcomas within the Sarcoma MDT.
- Morcellation of a uterine sarcoma is associated with higher rates of abdomino-pelvic recurrence, and poorer progression free and overall survival than definitive surgery with hysterectomy. It is therefore contra-indicated for uterine sarcoma.
- The gynaecological oncology team has the site specific expertise to deliver the majority of local treatments including surgery and radiotherapy.
- Pathology of sarcoma is specialised.

#### **9.1.2 Diagnoses requiring discussion at the Sarcoma MDT**

## **Suggested gynaecological sarcoma diagnoses for discussion at the Sarcoma MDT:**

- Adenosarcoma with sarcomatous overgrowth
- Low grade endometrial stromal sarcoma
- High grade endometrial stromal sarcoma
- Undifferentiated uterine sarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Any extrauterine, disseminated or unusual sarcoma

## **Cases not requiring Sarcoma MDT discussion:**

- Carcinosarcoma
- Adenosarcoma
- UTROSCT
- STUMP and variants of leiomyoma

### **9.1.3 Sampling and grading**

#### **Sampling**

- One block per cm recommended, for example to identify necrosis in smooth muscle tumours, epithelial elements (particularly if sarcoma is undifferentiated or includes heterologous elements), or to identify high grade areas.

#### **Grading**

- There is no formal grading system for uterine leiomyosarcomas but oncologists often ask for a grade and the choice of adjuvant therapy may depend on whether the neoplasm is 'high' or 'low' grade.
- At present, there is no evidence that the Trojani grading system is of prognostic significance in uterine leiomyosarcomas; only a single study has evaluated this grading system in uterine sarcomas and found that this system could not be used as a prognostic indicator. In this study, stage and mitotic count were the only factors that had an influence on survival and relapse of uterine leiomyosarcomas.
- A note should be included in the pathology report that this is intended only as a general guide to management and is not evidence-based.

### **9.1.4 Principles of management**

The following principles underpin these recommendations:

- As sarcomas are rare, a high index of suspicion may be helpful
- All patients with a suspected or proven sarcoma presenting to the local gynaecology MDT should be referred to the Sarcoma MDT for discussion wherever possible before treatment
- There is uncertainty about aspects of treatment for gynaecological sarcoma. Discussion of treatment between the sarcoma and gynaecological MDT is likely to improve mutual understanding and thereby treatment and outcomes for patients.

- Sarcoma histopathology is specialised and therefore review by the sarcoma expert pathologist to confirm the diagnosis is important.
- Surgery should be carried out by the most appropriate surgical team (usually the gynaecology oncology team after discussion). Particular issues which arise and may benefit from discussion include the need for lymphadenectomy and/or the resection of major organs.
- Radiotherapy is usually best delivered by the gynaecological oncology team who have site-specific expertise after discussion with sarcoma clinical oncologists
- Chemotherapy to be delivered by the most appropriate team after discussion
- The more common uterine sarcomas (leiomyosarcoma, endometrial stromal sarcoma, undifferentiated sarcoma or adenosarcoma) may be included as notations at sarcoma MDTs
- There should be close collaboration for disseminated uterine sarcomas and sarcomas of a morphological type other than the more common sarcomas listed in the previous point
- Patients with sarcoma should have access to good information and clinical trials
- After treatment patients should have access to appropriate follow up
- Patients with suspected relapse should be discussed as soon as possible and before treatment
- Close collaboration between sarcoma and gynaecological MDTs is particularly important in the management of extra-uterine gynaecological sarcomas which are not included in the Dataset for uterine sarcoma and the recommendation is to consult the latest publications.

### 9.1.5 Summary of roles and responsibilities of MDTs

	Role and responsibility	
	Specialist gynaecology MDT	Sarcoma MDT
<b>Presentation</b>	Identify new cases of suspected or proven gynaecological sarcoma as early as possible.	
<b>Diagnosis</b>	Refer all cases of gynaecological sarcoma for pathology review.  Refer new or proven cases for review by Sarcoma MDT and provide adequate information for discussion.  Perform appropriate local and systemic staging investigations	Review pathology of all new cases of gynaecological sarcoma ( <i>excluding carcinosarcoma and adenosarcoma as detailed above</i> ).  Discuss new sarcoma cases at MDT and provide prompt feedback.
<b>Treatment - surgical</b>	Most surgery will be performed by members of the gynaecology	Support the delivery of good surgical care through open

	MDT. However, complex cases, for example those involving multiple organ resection should be discussed.	discussion. Perform surgery where appropriate after discussion.
<b>Treatment - chemotherapy</b>	Deliver chemotherapy for sarcoma after discussion with Sarcoma MDT.	Deliver chemotherapy for sarcoma patients after discussion where appropriate.

<b>Treatment - radiotherapy</b>	Deliver radiotherapy for sarcoma after discussion with Sarcoma MDT.	Provide advice and support for decision making and treatment planning. Deliver radiotherapy after discussion if appropriate.
<b>Patient support and information</b>	Provide appropriate sarcoma and site specific information for patients treated under the gynaecology MDT.	Provide appropriate sarcoma and site specific information for patients treated under the Sarcoma MDT.
<b>Clinical trials</b>	Identify and encourage recruitment to relevant clinical trials.	Identify and encourage recruitment to relevant clinical trials.
<b>Follow up</b>	<p>Appropriate follow up of patients treated in the gynaecological service, considering survivorship and risk of local and systemic recurrence.</p> <p>Identify local or systemic relapse and refer to Sarcoma MDT before treatment.</p>	<p>Appropriate follow up of patients treated in the sarcoma service, considering survivorship and risk of local and systemic recurrence.</p> <p>Identify local or systemic relapse and refer to gynaecological MDT if appropriate.</p>
<b>Palliative/supportive care</b>	Identify and refer patients in need of palliative or supportive care under treatment by the gynaecological MDT.	Identify and refer patients in need of palliative or supportive care under treatment by the Sarcoma MDT.

## **9.1.6 Uterine leiomyosarcoma**

### **9.1.6.1 Diagnosis and staging**

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

### **9.1.6.2 Treatment of localised disease**

- Surgery – total abdominal hysterectomy and bilateral salpingo-oophorectomy. Oophorectomy may be avoided in pre-menopausal women. No indication for routine pelvic lymphadenectomy. Bulky or suspicious pelvic or para-aortic nodes should be removed.
- 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)

### **9.1.6.3 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.

#### **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.

## **9.1.7 Endometrial stromal sarcoma**

### **9.1.7.1 Diagnosis and staging**

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

### **9.1.7.2 Treatment of localised disease**

- Surgery – total abdominal hysterectomy and bilateral salpingo-oophorectomy. Bulky or suspicious pelvic or para-aortic nodes should be removed. 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.

### **9.1.7.3 Treatment of metastatic disease**

#### **Surgery**

Low grade 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. Metastatic high grade endometrial stromal sarcoma should be treated as for undifferentiated endometrial sarcoma (see 9.1.8.3).

#### **Hormonal therapy**

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

#### **Chemotherapy**

If hormonal therapeutic options have been exhausted, palliative chemotherapy can be considered.

## **9.1.8 Undifferentiated endometrial sarcoma**

### **9.1.8.1 Diagnosis and staging**

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

### **9.1.8.2 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 and bilateral salpingo-oophorectomy. Bilateral oophorectomy may be avoided in pre-menopausal women. No indication for routine pelvic lymphadenectomy. Bulky or suspicious pelvic or para-aortic nodes should be removed.
- Consider adjuvant doxorubicin and ifosfamide chemotherapy in young fit patients.
- Adjuvant pelvic radiotherapy may be considered

### **9.1.8.3 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.

## **9.2 Breast sarcomas**

Breast sarcomas are most likely to be diagnosed within the site-specific breast MDT. These should also be discussed within the Sarcoma 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 phylloides tumours

### **9.2.1 Diagnosis and staging**

- Pathology review
- Mammograms/breast MRI
- CT thorax

### **9.2.2 Treatment of localised disease**

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 in the neo-adjuvant setting.
- The local treatment of angiosarcoma is wide resection if feasible and such patients are usually best managed by members of the Sarcoma MDT.

### **9.2.3 Treatment of metastatic disease**

This is as for metastatic soft tissue sarcoma at other sites.

### **9.3 Head and neck sarcoma**

#### **9.3.1 Background**

- Head and neck sarcomas account for less than 10% of STSs and <1% of all non-cutaneous head and neck cancers. Tumour subtype is highly diverse.
- Therefore these cancers are rare even for high caseload head and neck malignancy specialist MDTs.
- Anecdotally patients with head and neck sarcoma do comparatively worse than equivalent staged disease of the trunk and extremity.
- The concentration of numerous tissue types in a relatively confined anatomical region is thought to contribute to higher local recurrence rates and difficulties in obtaining adequate margins of excision.
- It is probable previously reported rates of local recurrence and mortality were skewed by debulking rather than wide margin surgical excisions. Plus, concerns regarding reconstruction of functional loss, potentially complex and composite defects, may inhibit appropriate surgical excision of certain tumours.
- More recent retrospective appraisals in the UK have illustrated favourable local recurrence rates and 5 year disease free survival is estimated at 72%.
- It is therefore suggested that head and neck sarcomas are treated by head and neck surgeons within regional sarcoma services who are also part of regional head and neck services where possible, to maximise access to optimal resection and reconstructive capabilities.
- Radiotherapy and chemotherapy should be considered in all high grade cases regardless of tissue type (i.e. including head and neck skin sarcomas). Given probably higher local recurrence rates in the head and neck, neoadjuvant therapies should be discussed where it is felt morbidity will be tolerated.
- The rarity of this group of sarcomas may in the future require supra-regional services to concentrate expertise and improve outcomes. This is expected in the 2017 national service specifications.

#### **9.3.2 Principles of management**

- All patients with a suspected or proven sarcoma presenting to a head and neck MDT and/or specialist skin MDT should be referred to the regional sarcoma MDT.
- Head and neck surgeons that are part of both head and neck/sarcoma MDTs should co-ordinate and provide surgical expertise in conjunction with head and neck team members where required. This model will likely maintain and improve upon current favourable surgical outcomes. Involvement of craniofacial/skullbase expertise should be sought in specific cases where necessary.
- Sarcoma histopathology must be reviewed by the sarcoma specialists.
- Radiotherapy can be delivered by head and neck or sarcoma specific oncology teams.
- Chemotherapy can be delivered by whichever team is deemed more appropriate following MDT discussion.
- Nurse specialist, speech and language therapy and dietician expertise can be accessed where needed.

### 9.3.3 Summary of roles and responsibilities of MDTs

	Role and responsibility	
	Specialist Head and Neck MDT	Sarcoma MDT
Presentation	Identify new cases of suspected or proven sarcoma.	Identify new cases of suspected or proven sarcoma.
Diagnosis	<p>Refer all cases of sarcoma for pathology review.</p> <p>Refer new or proven cases for review by sarcoma MDT and provide adequate information for discussion.</p> <p>Perform appropriate local and systemic staging investigations</p>	<p>Review pathology of all new cases of sarcoma.</p> <p>Discuss new sarcoma cases at MDT and provide prompt feedback.</p> <p>Discuss cases and head and neck MDT that require surgical expertise to improve surgical outcome in conjunction with sarcoma head and neck surgeons.</p>
Treatment - surgical	Surgery will be performed by members of the head and neck and sarcoma services. Plus surgical colleagues where complex tumours involving mediastinum/chest requires specific expertise.	Surgery will be performed by members of the head and neck and sarcoma services. Plus surgical colleagues where complex tumours involving mediastinum/chest, skull base requires specific expertise.
Treatment - chemotherapy	Deliver chemotherapy for sarcoma after discussion with Sarcoma MDT. This can be done locally depending on patient preference and local availability of services.	Deliver chemotherapy for sarcoma after discussion with Sarcoma MDT. This can be done locally depending on patient preference and local availability of services.

Treatment - radiotherapy	Deliver radiotherapy for sarcoma after discussion with Sarcoma MDT. This can be done locally/by site specific depending on patient preference and local availability of services.	Deliver radiotherapy for sarcoma after discussion with Sarcoma MDT. This can be done locally/site specific depending on patient preference and local availability of services.
Patient support and information	Provide appropriate sarcoma and site specific information for patients treated. This may include access to allied healthcare members of the head and neck team. (Dentistry, dietician, speech and language, specialist nurses, psychology)	Provide appropriate sarcoma and site specific information for patients treated. This may include access to allied healthcare members of the head and neck team. (Dentistry, dietician, speech and language, specialist nurses, psychology)
Clinical trials	Identify and encourage recruitment to relevant clinical trials.	Identify and encourage recruitment to relevant clinical trials.
Follow up	Follow-up in sarcoma and/or head and neck clinics. Identify local or systemic relapse and refer to sarcoma MDT before treatment.	Follow-up in sarcoma and/or head and neck clinics. Identify local or systemic relapse and refer to sarcoma MDT before treatment.
Palliative/supportive care	Identify and refer patients in need of palliative or supportive care under treatment by the head and neck/sarcoma MDT.	Identify and refer patients in need of palliative or supportive care under treatment by the head and neck/sarcoma MDT.

#### **9.3.4 Diagnosis and staging**

- Pathology review
- MRI head and neck
- CT head neck and thorax
- Other staging (e.g. PETscan) as indicated.

#### **9.3.5 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.
- A clear plane of uninvolved fascia/muscle deep to tumour is appropriate for cutaneous and non-cutaneous head and neck sarcomas.
- In tumour sub-types that are not radio or chemo sensitive wide ablation where feasible should be offered.
- Diffuse tumour types, dependent on location, can be excised and definitive reconstruction can be delayed until urgent histopathology has confirmed complete excision. Thereby preventing complex reconstruction over possible microscopic residual disease.

#### **9.3.6 Treatment of metastatic disease**

- See tumour-specific sections above.
- Debulking surgery and reconstruction of patients presenting with extensive disease that threatens airway, major function, major vasculature and skin fungation can be offered where appropriate following discussion at head and neck/sarcoma MDTs and the patient. Or when palliative radio/chemotherapy is not an option.

## 9.4 Sarcomas of the skin

### 9.4.1 Diagnosis and staging

The skin sarcomas include:

- Leiomyosarcoma (LMS)
- Dermatofibrosarcoma protuberans (DFSP)
- Kaposi sarcoma (KS)
- Cutaneous angiosarcoma (CA)
- Myxofibrosarcoma (MS)
- Pleomorphic dermal sarcoma (PDS)

Skin sarcomas are rare and vary widely in clinical presentation and pathological features. The clinical features are often not characteristic. They share a high rate of local recurrence after excisional surgery and some have a high rate of metastasis (subcutaneous LMS, CA, MS & PDS).

The evidence base is limited given the rarity of the tumours and is mostly limited to retrospective case series and case reports.

#### **Leiomyosarcoma (LMS)**

This section only refers to LMS of the skin or subcutis. LMS deep to or involving the investing fascia should be managed as soft tissue sarcomas within the Sarcoma MDT. Local recurrence rates following wide excision for cutaneous LMS vary from 25-50% and for subcutaneous LMS are 50%. Cutaneous LMS does not metastasize, whereas LMS in the subcutis has a high risk of metastasis (over 30%). Large tumours (over 4cm diameter) are very likely to involve the subcutis and therefore have metastatic potential. Superficial biopsy is not adequate in determining the depth of tumour involvement.

**Dermatofibrosarcoma protuberans** has a number of clinical and histological subtypes including;

- Myxoid
- Atrophic
- Pigmented (Bednar tumour)
- Fibrosarcomatous
- Giant cell fibroblastoma (in children)

10 to 15% of DFSP are fibrosarcomatous (DFSP-FS) and have metastatic potential (around 5%). Fibrosarcomatous changes are more common in recurrent DFSP. DFSP-FS should have staging and management within the Sarcoma MDT.

Mohs micrographic surgery (MMS) or wide local excision may be considered as a first-line therapy for non-sarcomatous DFSP. The appropriateness of each approach is likely to depend on the patient, and the anatomical location of the tumour. Therefore discussion in both MDTs is encouraged to allow the patient the benefit of the expertise of both.

**Kaposi sarcoma** is managed within an extended skin cancer MDT team, including infectious disease (ID) team lead by Dr Ashley Price, and radiotherapy. This has been previously agreed within the skin cancer MDT and offered as a service across the cancer network.

**Angiosarcoma** usually requires aggressive surgery and consideration of systemic treatment. Therefore management is most appropriate within the Sarcoma MDT, usually by the plastic surgical team.

**Pleomorphic dermal sarcoma** was previously known as malignant fibrous histiocytoma. Atypical fibroxanthoma is considered a less aggressive superficial variant of pleomorphic dermal sarcoma without metastatic potential.

#### **9.4.2 Treatment**

- There should be a low threshold for discussion of patients with sarcomas of the skin in both MDTs, particularly where there is uncertainty about diagnosis or treatment
- Patients with Kaposi's sarcoma and those with LMS not involving the subcutis are appropriately managed by the normal and extended skin cancer MDT and do not have to be routinely discussed at the Sarcoma MDT
- Any patient with a sarcoma involving the subcutis should be referred to and managed by the Sarcoma MDT
- Low grade dermatofibrosarcoma protuberans (DFSP) may be managed by the skin cancer MDT or the Sarcoma MDT. As the approach to local treatment may differ, discussion in both MDTs is recommended and outcomes should be audited.
- DFSP with fibrosarcomatous change (DFSP-FS) should be managed by the Sarcoma MDT
- Patients with angiosarcoma, myxofibrosarcoma or pleomorphic dermal sarcoma should be managed by the Sarcoma MDT

## 10 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. The Sarcoma MDT has agreed to follow the European consensus statement on fibromatosis<sup>7</sup>.

The possibility that fibromatosis may be associated with Familial Adenomatous Polyposis (FAP) should be considered.

### 10.1 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.

### 10.2 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.

## 11 Neurofibromatosis

### 11.1 Referral of Patients with Neurofibromatosis to Northern Genetics Service

The NF team comprises the following:

Consultant clinical geneticist: Dr Miranda Splitt [Miranda.splitt@nuth.nhs.uk](mailto:Miranda.splitt@nuth.nhs.uk)

0191 241 8741

NF Specialist Nurse: Mrs Susan Musson [susan.musson@nuth.nhs.uk](mailto:susan.musson@nuth.nhs.uk)

0191 2418732/07543308416

Mrs Rachel Jones [Rachel.jones@nuth.nhs.uk](mailto:Rachel.jones@nuth.nhs.uk)

01912418732/07747898489

#### 11.1.1 Patients with Plexiform Neurofibromas seen by Sarcoma Team

NGS maintains a register of all patients with NF1. All patients with high burden or 'complex' disease are kept under review by the Complex NF1 HSS based in Manchester. Please copy Susan Musson and Rachel Jones, NF1 Specialist Nurses, into all correspondence regarding any patient seen with a plexiform. They can check whether patient is known to Genetics and if not arrange Genetics Review and offer family assessment.

Neurofibromatosis Specialist Nurses

Institute of Genetic Medicine

International Centre for Life

Newcastle Upon Tyne Hospitals NHS Trust

NE1 3BZ

#### 11.1.2 Patients with multiple schwannomas seen by sarcoma team

Patients with more than one schwannoma may be at risk of other NF2 related tumours or may have familial schwannomatosis and thus warrant assessment by a clinical geneticist. Please refer any patient with more than one schwannoma to:

Dr Miranda Splitt

Consultant in Clinical Genetics

Institute of Genetic Medicine

International Centre for Life

Newcastle Upon Tyne Hospitals NHS Trust NE1 3BZ

### 11.2 Referral of NF1 patients from Genetics to Sarcoma Team (Mr Craig Gerrand, Mr Tom Beckingsale, Mr Kenneth Rankin)

#### 11.2.1 NF1 patients with suspected MPNSTs

NF1 patients with signs/ symptoms which are suggestive of an MPNST should be referred urgently to the sarcoma team by means of emailed referral letter and MDT proforma. These patients will be reviewed urgently by the sarcoma team and discussed at the sarcoma MDT.

#### 11.2.2 NF1 patients with symptoms where cause is unclear

These patients should be assessed by the Genetics Team and if appropriate MRI scans requested. If plexiform NF identified on MRI they should be referred to the sarcoma team who will review at Sarcoma MDT and decide management and most appropriate surgical specialty.

### **11.2.3 NF1 Patients who have/ have had Atypical Plexiform Neurofibromas**

These patients should be kept under review by the sarcoma team.

### **11.2.4 Children with Large/Enlarging Plexiform neurofibromas**

Should be referred to the Sarcoma Team and followed up in the Paediatric sarcoma clinic.

## **12 References**

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