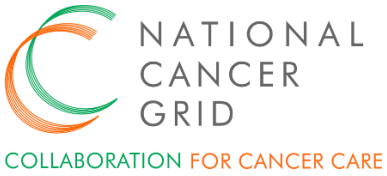


NCG GUIDELINES- 2019
Bone and Soft Tissue Tumors Management Guidelines

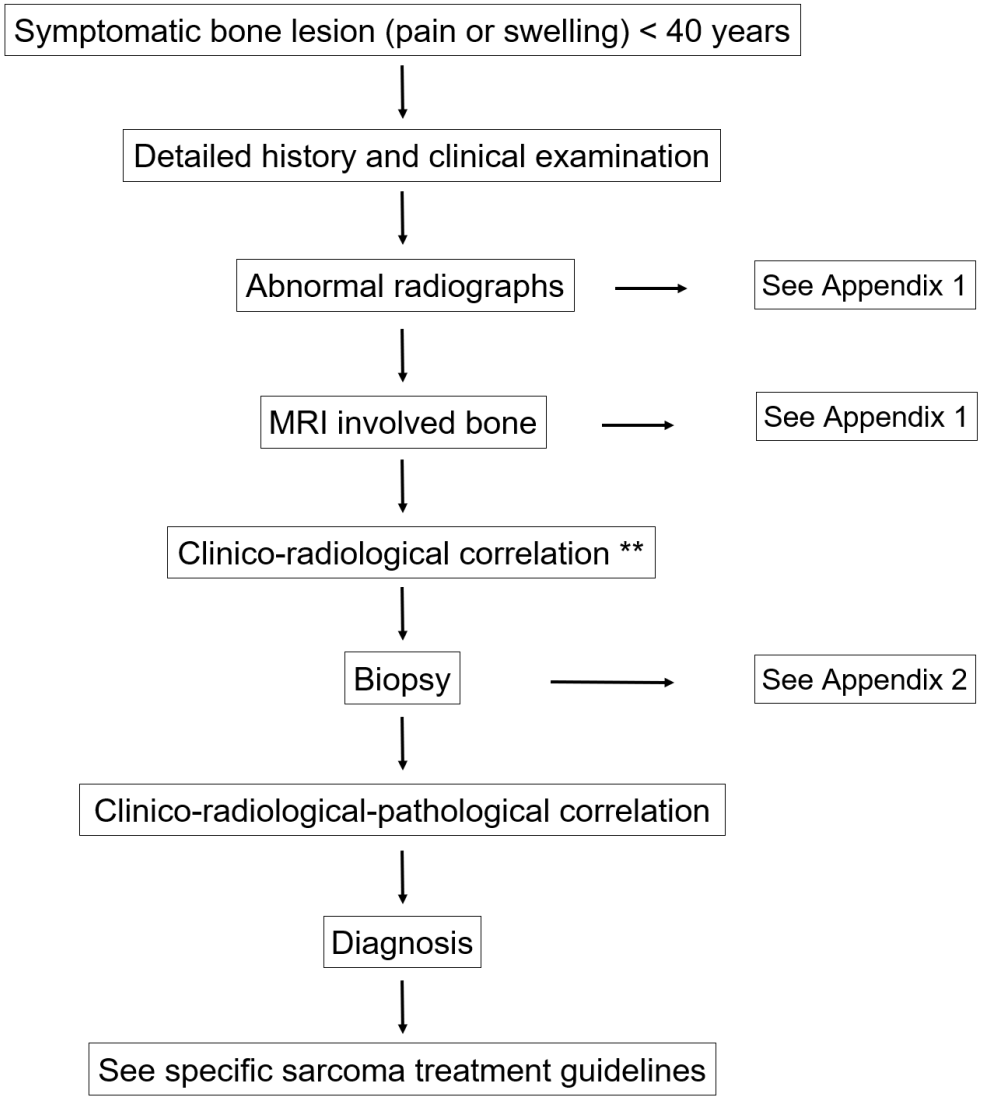
Categories of the guidelines

a) Essential
b) Optimal
c) Optional

**Herewith essential will be referred as (a), optimal as (b) and optional as (c)*

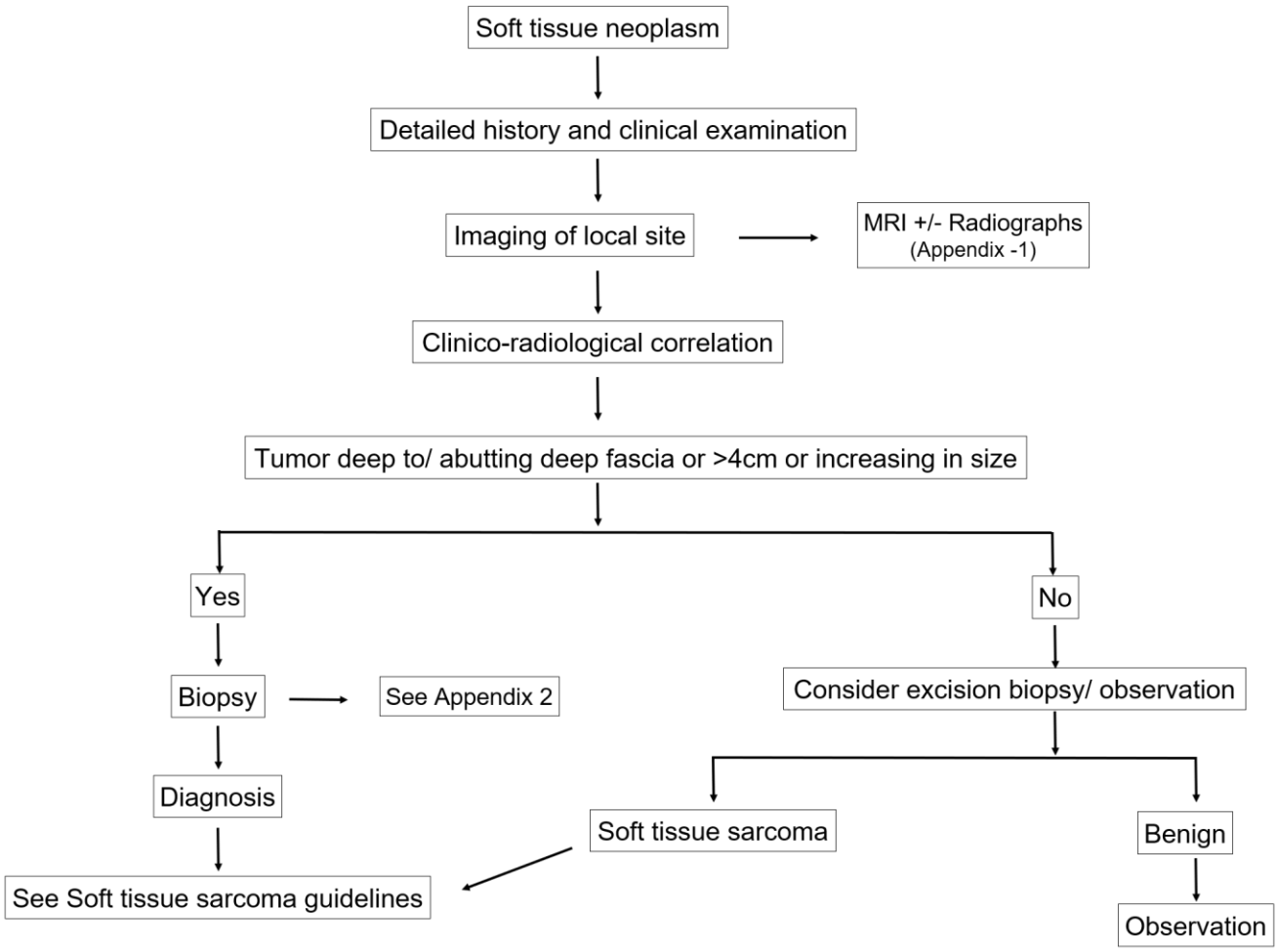
Content

EVALUATION OF SUSPECTED BONE SARCOMA

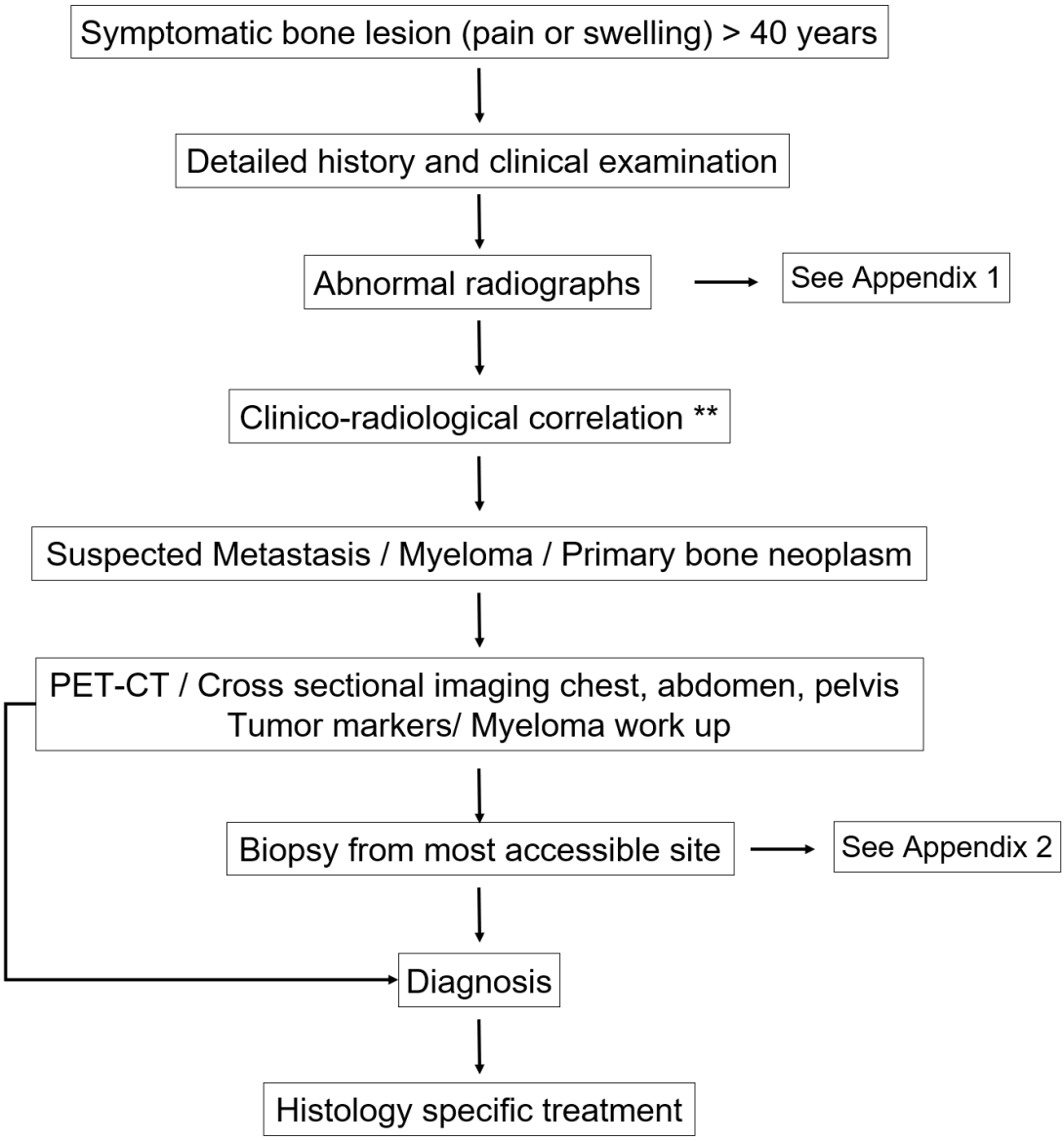


***** Please note that pathological fracture is not an emergency for internal fixation***

EVALUATION OF SUSPECTED SOFT TISSUE SARCOMA



EVALUATION OF SUSPECTED METASTATIC BONE DISEASE



***** Please note that pathological fracture is not an emergency for internal fixation***

OSTEOSARCOMA

Symptoms – swelling & pain

↓

Detailed clinical history

↓

Clinical diagnosis

↓

Workup for diagnosis

Basic imaging (local & chest x-ray) & routine blood investigations (a)

↓

Local 3D imaging - MRI (with contrast) of entire bone with adjoining joints (a)

OR - Local imaging - X ray and Dynamic Contrast MRI with Diffusion (b)

Additional serological investigations (alkaline phosphatase and lactate dehydrogenase) (a)

↓

Clinico- radiological diagnosis

↓

Biopsy (core needle biopsy preferred) (a)
(Appendix 3 for principles of biopsy)

↓

Histopathological diagnosis (Use of Immunohistochemistry where applicable- (c)

↓

Workup for Staging

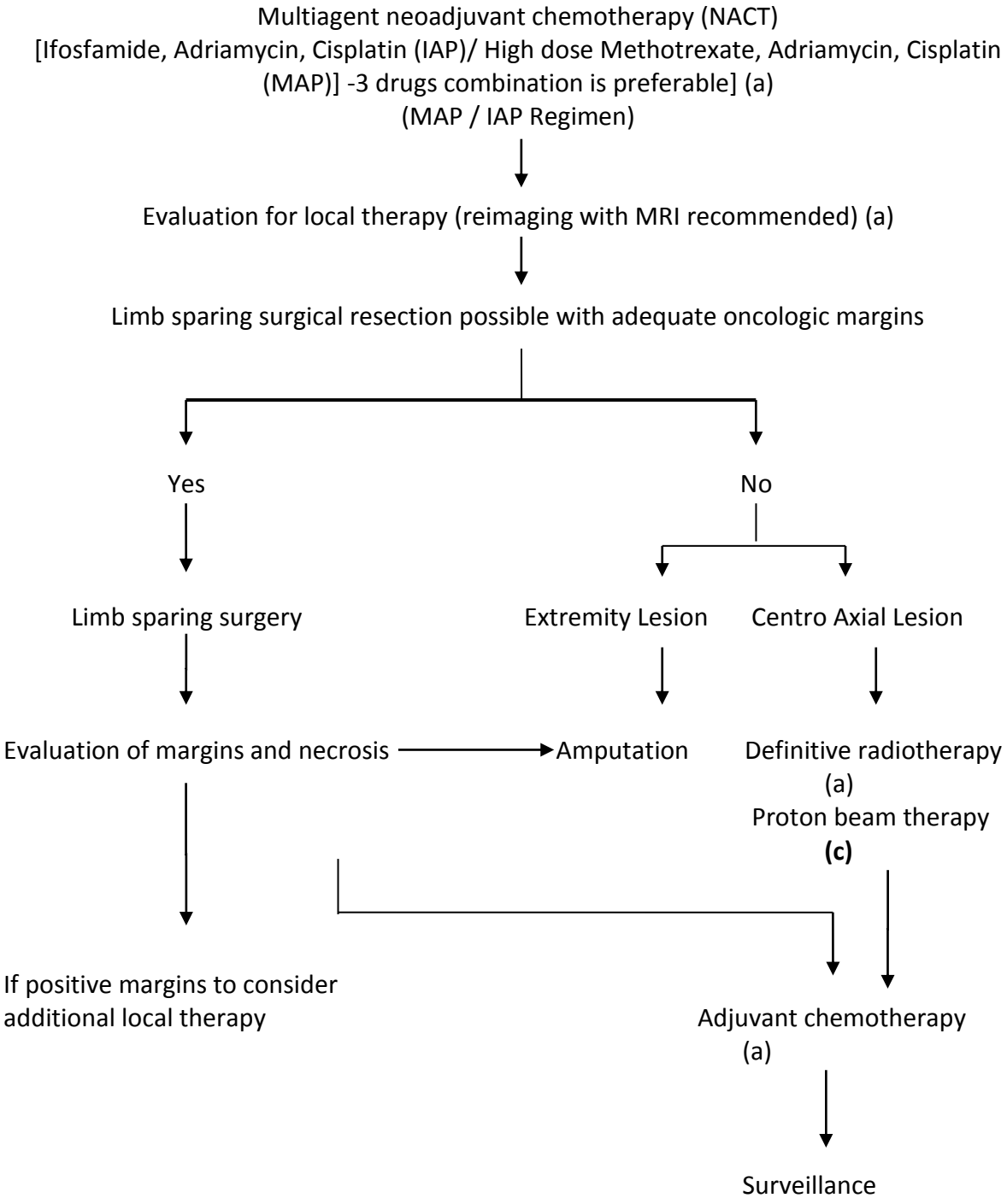
(NCCT scan chest & Bone scan) (a)

Or - (c) -F_{18} PET/EDF PET -with breath hold chest CT Scan)

↓

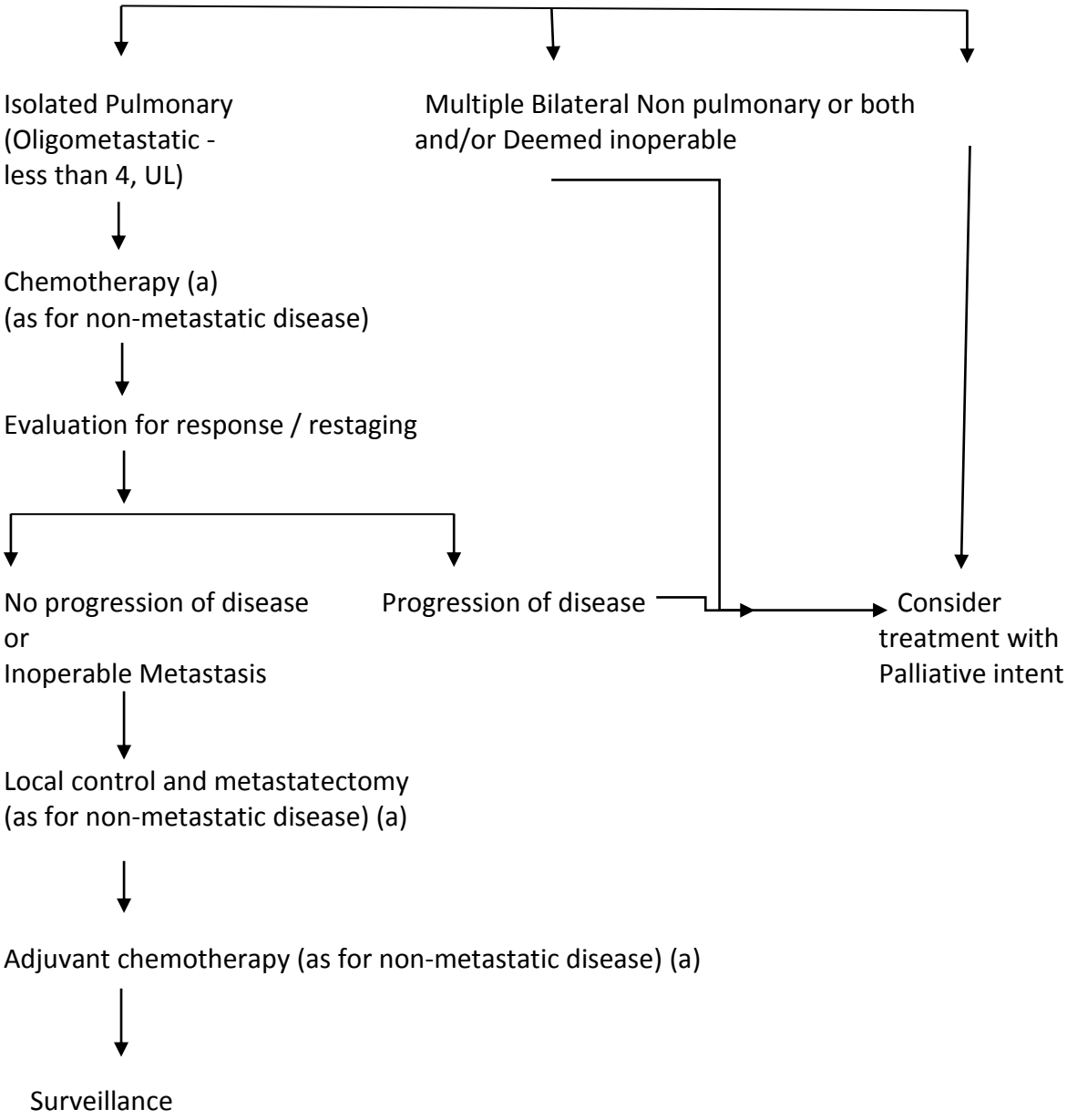
Non-metastatic Osteosarcoma | **Metastatic Osteosarcoma**

OSTEOSARCOMA NON-METASTATIC PRESENTATION



- MAP regimen should only be administered in centers with adequate facility for monitoring Methotrexate levels.

OSTEOSARCOMA METASTATIC AT PRESENTATION



- May consider palliative chemotherapy with 2 agents (cisplatin & doxorubicin) to avoid toxicity and palliative radiotherapy for relieving pain.
- Decision for palliative intent of treatment should be taken after discussion in multi-disciplinary tumor board. The intent of treatment can change from palliative to curative or vice-versa based on the patient's clinical condition.

CHEMOTHERAPY FOR OSTEOSARCOMA

Regimen	Schedule
Cisplatin + doxorubicin	Days 1–3: Doxorubicin 25mg/m^2/day IV over 2 hours, plus Day 1: Cisplatin 100mg/m^2 IV over 3 hours Repeat cycle every 3 weeks for 6 cycles.
MAP (high-dose methotrexate + cisplatin + doxorubicin)	**Neoadjuvant (week 1-10/2 cycles)** Cisplatin 120 mg/m² (4 h infusion of 60 mg/m² per day for 2 days) and doxorubicin 37·5 mg/m² per day on days 1 and 2 as 4-hour infusion (on weeks 1 and 6). This is followed by high-dose methotrexate 12 g/m² over 4 h (maximum dose 20 gm) with hyper-hydration, alkalinisation, and standard leucovorin rescue at a dose of 15 mg/m² (weeks 4, 5, 9, and 10). **Adjuvant chemotherapy (week 12-29/4 cycles)** Cisplatin 120 mg/m² (4 h infusion of 60 mg/m² per day for 2 days) (on week 12 and 17). Doxorubicin 37·5 mg/m² per day on days 1 and 2 as 4-hour infusion (on week 12, 17, 22 and 26). High-dose methotrexate 12 g/m² over 4 h (maximum dose 20 gm) with hyper-hydration, alkalinisation, and standard leucovorin rescue at a dose of 15 mg/m² (weeks 15, 16, 20, 21, 24, 25, 28, 29).
Ifosfamide, Adriamycin and Cisplatin (IAP)	Ifosfamide 1.3 gm/m^2 day 1,2 and 3 Adrimaycin 50 mg/m^2 day 1 Cisplatin 100 mg/m^2 divided over day 1-3

Salvage/Second-line chemotherapy* - Second-line chemotherapy for patients with relapsed/refractory disease is given below).

Regimen	Schedule
Gemcitabine + docetaxel (a).	Days 1 and 8: Gemcitabine 675mg/m^2 IV, plus Day 8: Docetaxel 75–100mg/m^2 IV. Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).
Carboplatin + ifosfamide + etoposide (a).	Days 1 and 2: Carboplatin 400mg/m^2/day IV, plus Days 1–5: Ifosfamide 1,800mg/m^2/day IV + mesna + etoposide 100mg/m^2/day IV. Repeat cycle every 3 weeks for up to 12 cycles
Cyclophosphamide + topotecan (a).	Days 1–5: Cyclophosphamide 250mg/m^2 IV over 30 minutes Days 1–5: Topotecan 0.75mg/m^2 IV over 30 minutes Repeat cycle every 3 weeks for 12–14 cycles.
Ifosfamide (high dose) ± etoposide (a).	Days 1–5: Ifosfamide 1,800mg/m^2/day IV + mesna, plus Days 1–5: Etoposide 100mg/m^2/day IV. Repeat every 3 weeks for 12 cycles.

The choice of regimen in second line therapy should be based on patient profile and drugs used previously.

RADIOTHERAPY FOR OSTEOSARCOMA

Doses and technique

1. Definitive RT up to doses of ≥70Gy@ 1.8-2Gy/# to be considered (a).
2. Conformal portals, adaptive planning and image guidance is recommended (a).
3. Select cases to be considered for particle beam therapy (c).

EWING's SARCOMA

Symptoms – swelling & pain

↓

Detailed clinical history

↓

Clinical diagnosis

↓

Workup for diagnosis

Basic imaging (local & chest x-ray) & routine blood investigations (a)

↓

Local 3D imaging - MRI (with contrast) of entire bone with adjoining joints (a)

OR - Local imaging - X ray and Dynamic Contrast MRI with Diffusion **(b)**

Additional serological investigations (alkaline phosphatase and lactate dehydrogenase) (a)

↓

Clinico-Radiological diagnosis

↓

Biopsy (core needle biopsy preferred) (a)
(Appendix 3 for principles of biopsy)

↓

Histopathological diagnosis with IHC (a) AND Molecular Pathology (**c**)

↓

Workup for Staging

Non-Contrast Computed Tomography of Chest AND Bone Scan AND Bone Marrow Aspiration (2 sites-Bilateral) (a)

OR

FDG PET Scan with Breath Hold CT Chest (a)

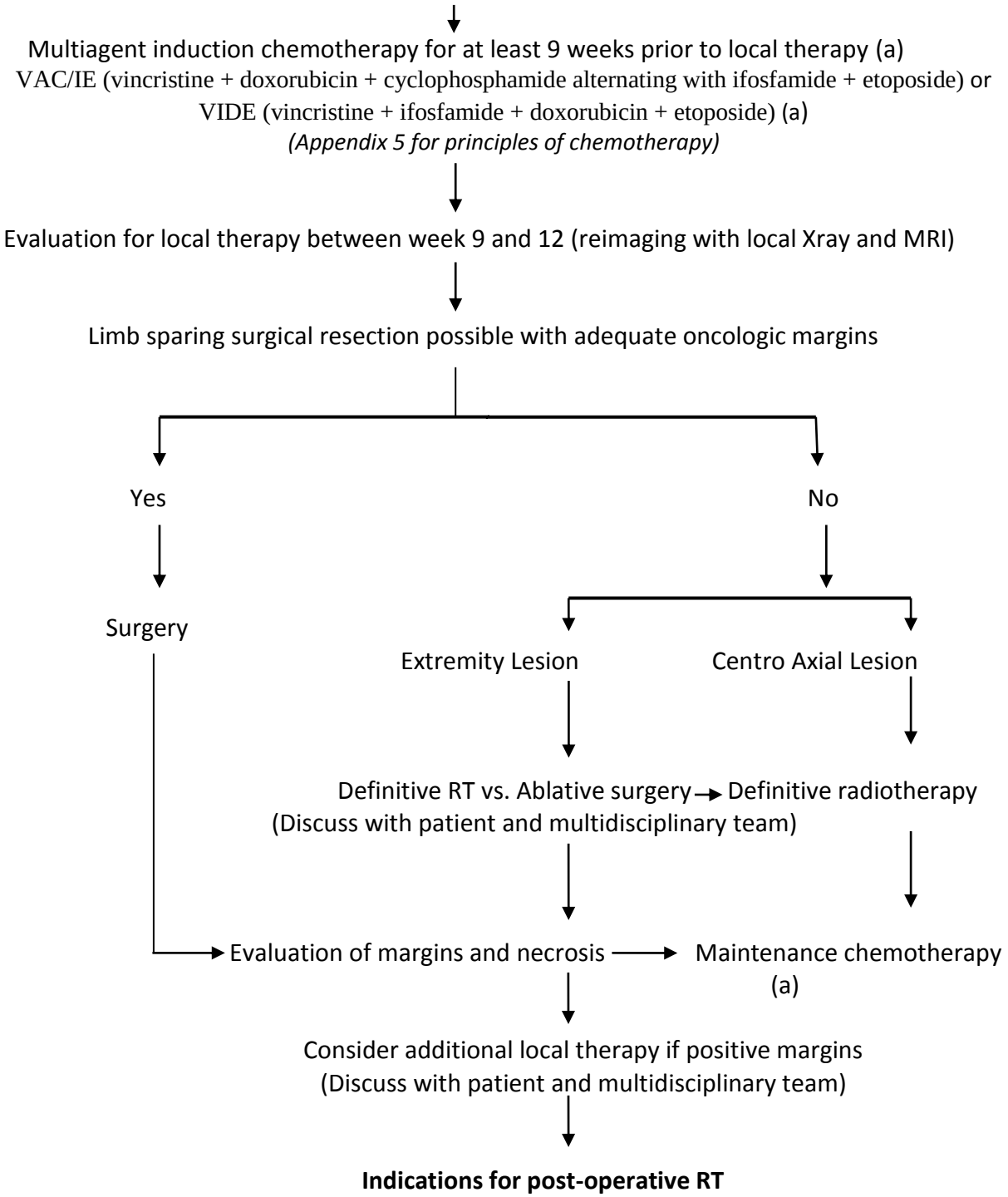
OR

Non-Contrast Computed Tomography of Chest AND MRI Whole Body **(c) -special situations like pregnancy)**

↓

Non-metastatic Ewing's sarcoma | **Metastatic Ewing's sarcoma**

EWING'S SARCOMA - NON-METASTATIC AT PRESENTATION



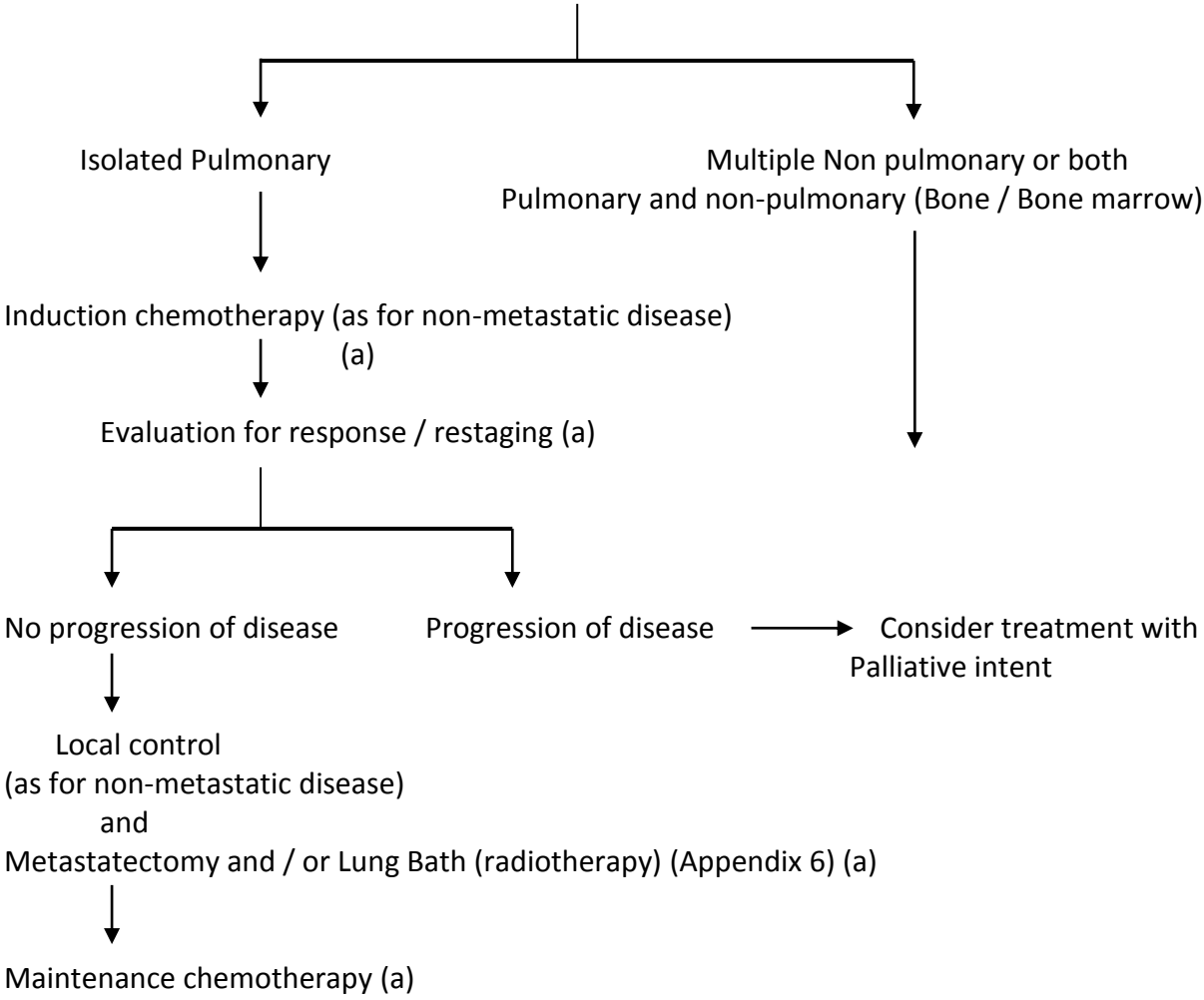
Indications for post-operative RT

Adjuvant RT to be **strongly considered** in -(Appendix 6) (a)

- Sites- Spinal/ Paraspinal / pelvic location (Difficult to achieve adequate margins due to complex anatomy)
- Large tumor volume >300 cc
- Pathological fracture

Negative Margins		Positive margins
> 90 % necrosis	No adjuvant RT	Adjuvant RT
< 90 % necrosis	Discuss in multidisciplinary clinic (MDJC)	Adjuvant RT

EWING's SARCOMA – METASTATIC AT PRESENTATION



CHEMOTHERAPY FOR EWING's SARCOMA

First-line non-metastatic disease (Neoadjuvant/Adjuvant) (a)

Regimen [reference]	Schedule
VAC/IE (vincristine + doxorubicin + cyclophosphamide alternating with ifosfamide + etoposide)	**Alternating VAC and IE cycles** *VAC cycles* **Day 1:** Vincristine 2 mg/m^2 (max 2mg) IV over 5-10 minutes **Day 1:** Doxorubicin 75mg/m^2 IVP or Dactinomycin 1250mcg/m^2 IVP (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m^2 has been met) **Day 1:** Cyclophosphamide 1200mg/m^2 IV over 60 minutes + Mesna *IE cycles* **Days 1-5:** Ifosfamide 1800 mg/m^2 IV over 3 hours + Mesna **Days 1-5:** Etoposide 100mg/m^2 IV over 60 minutes Repeat each cycle every 2 weeks or 3 weeks for 17 cycles
VIDE (vincristine + ifosfamide + doxorubicin + etoposide)	**Day 1:** Vincristine 1.5 mg/m^2 (max 2mg) IV push over 5-10 minutes **Days 1-3:** Ifosfamide 3g/mg^2 IV continuous infusion over 1-3 hours + Mesna (give concurrently with ifosfamide) **Days 1-3:** Doxorubicin 20mg/m^2 IV continuous infusion over 4 hours or Dactinomycin 500mcg/m^2 IV (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m^2 has been met) **Days 1-3:** Etoposide 150mg/m^2 IV over 1 hour Repeat cycle every 3 weeks for up to 6 cycles

Second-line treatment for relapsed/refractory disease (a)

Regimen [reference]	Schedule
Cyclophosphamide + topotecan	Days 1–5: Cyclophosphamide 250mg/m^2 IV over 30 minutes Days 1–5: Topotecan 0.75mg/m^2 IV over 30 minutes Repeat cycle every 3 weeks for 12-14 cycles
Irinotecan ± temozolomide	Days 1–5: Temozolomide 100mg/m^2/day orally, plus Days 1–5 and 8–12: Irinotecan 10–20mg/m^2/day IV at least 1 hour after temozolomide. Repeat cycle every 3 or 4 weeks.
Docetaxel + gemcitabine	Days 1 and 8: Gemcitabine 675mg/m^2 IV, plus Day 8: Docetaxel 75–100mg/m^2 IV. Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).

- Decision for palliative intent of treatment should be taken after discussion in multi-disciplinary tumor board. The intent of treatment can change from palliative to curative or vice-versa based on the patient's clinical condition.
- **The choice of regimen in second line therapy should be based on patient profile and drugs used previously.**

RADIOTHERAPY FOR EWING's SARCOMA

Adjuvant Radiotherapy (a)

Radiotherapy doses and technique

1. Margin negative R0 resection: 45Gy/25#s over 5 weeks (a)
2. Positive margin: R1 resection - 50.4Gy/28#s over 6 weeks, R2 resection - 55.8Gy/31#s over 6.5 weeks (a).

Definitive Radiotherapy (c)

Radiotherapy doses and technique - 55.8Gy/31#s over 6 weeks (a)

Lung bath (a)

The recommended dose for lung bath is 12.6Gy/7#s over 10 days with tailored portals (a).

RT in metastatic disease

1. RT may be preferred local treatment (for primary as well as the metastatic sites) in oligometastatic cases (c). Margin negative R0 resection: 45Gy/25#s over 5 weeks (a)
2. Positive margin: R1 resection - 50.4Gy/28#s over 6 weeks, R2 resection - 55.8Gy/31#s over 6.5 weeks (a).

Palliative RT

RT can be used for palliation of symptomatic sites (primary or metastatic or both) with dose fractionation depending upon tolerance and response (c).

CHONDROSARCOMA

Symptoms – swelling & pain

↓

Detailed clinical history

↓

Clinical diagnosis

↓

Workup for Diagnosis

Basic imaging (local & chest x-ray) & routine blood investigations (a)

↓

Local 3D imaging - MRI (with contrast) of entire bone with adjoining joints (a)

OR - Local imaging - X ray and Dynamic Contrast MRI with Diffusion **(b)**

↓

Clinico- radiological diagnosis

↓

Biopsy (core needle biopsy preferred) (a)
(Appendix 3 for principles of biopsy)

↓

Histopathological diagnosis

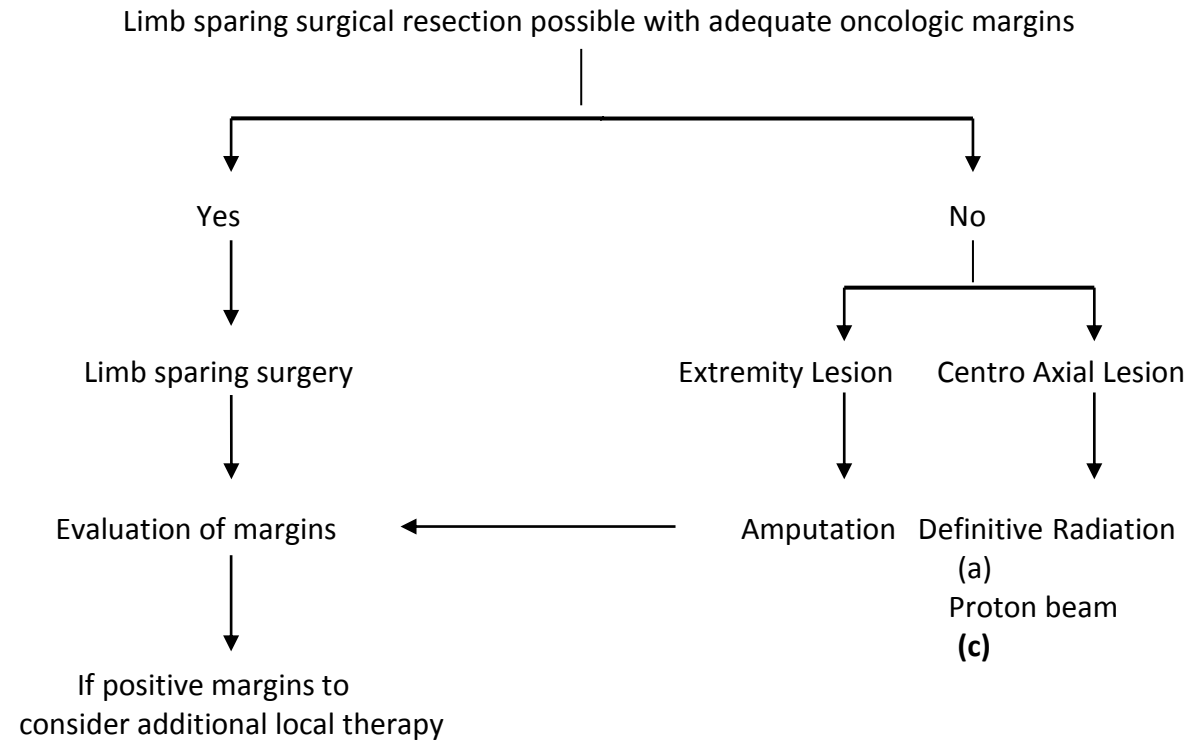
↓

Workup for Staging
(Local X ray & MRI & CT scan chest
Bone scan –(c) in primary cases)

↓

Non-metastatic chondrosarcoma | **Metastatic chondrosarcoma**

CHONDROSARCOMA - NON-METASTATIC AT PRESENTATION



CHONDROSARCOMA-METASTATIC AT PRESENTATION

RADIOTHERAPY FOR CHONDROSARCOMA

Doses and technique

1. Definitive RT up to doses of ≥70Gy@ 1.8-2Gy/# to be considered (a).
2. Conformal portals, adaptive planning and image guidance is recommended (a).
3. Select cases to be considered for particle beam therapy (c).

EXTREMITY SOFT TISSUE SARCOMA

Symptoms – swelling & pain

↓

Detailed clinical history and examination

↓

Clinical diagnosis

↓

Workup for Diagnosis
Basic imaging (local & chest x-ray, local MRI) & routine blood investigations (a)

↓

Clinico- radiological diagnosis

↓

Biopsy (core needle biopsy preferred) (a)

↓

Histopathological diagnosis

↓

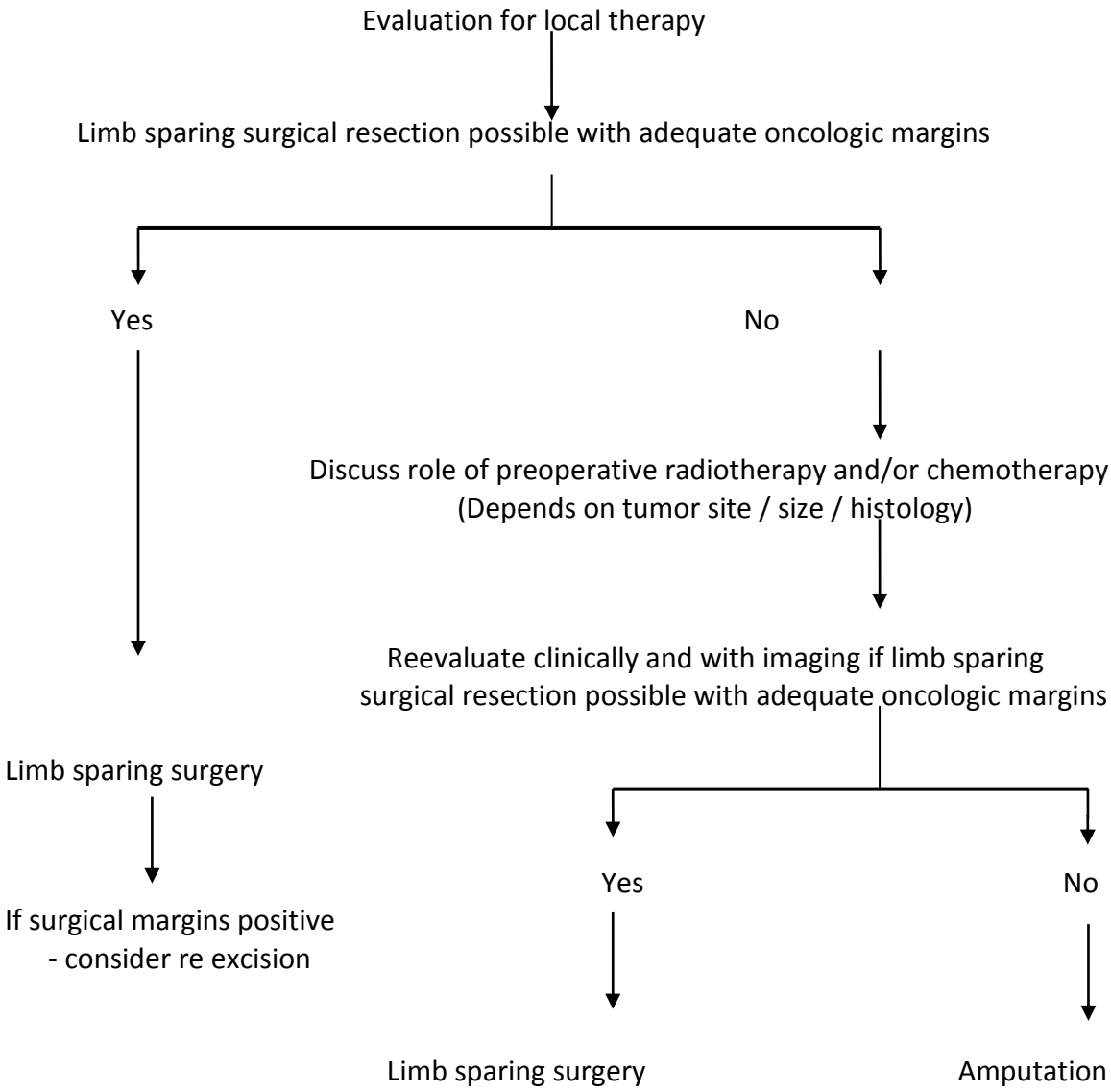
Workup for Staging
(Local X ray & MRI
NCCT scan chest & USG abdomen pelvis/groin/neck / axilla) (a)

↓

Non- metastatic soft tissue sarcoma | **Metastatic soft tissue sarcoma**

- Tumors referred after prior excision with inadequate or unknown margins need to be considered for re excision with similar guidelines as primary tumors

EXTREMITY SOFT TISSUE SARCOMA – NON-METASTATIC AT PRESENTATION



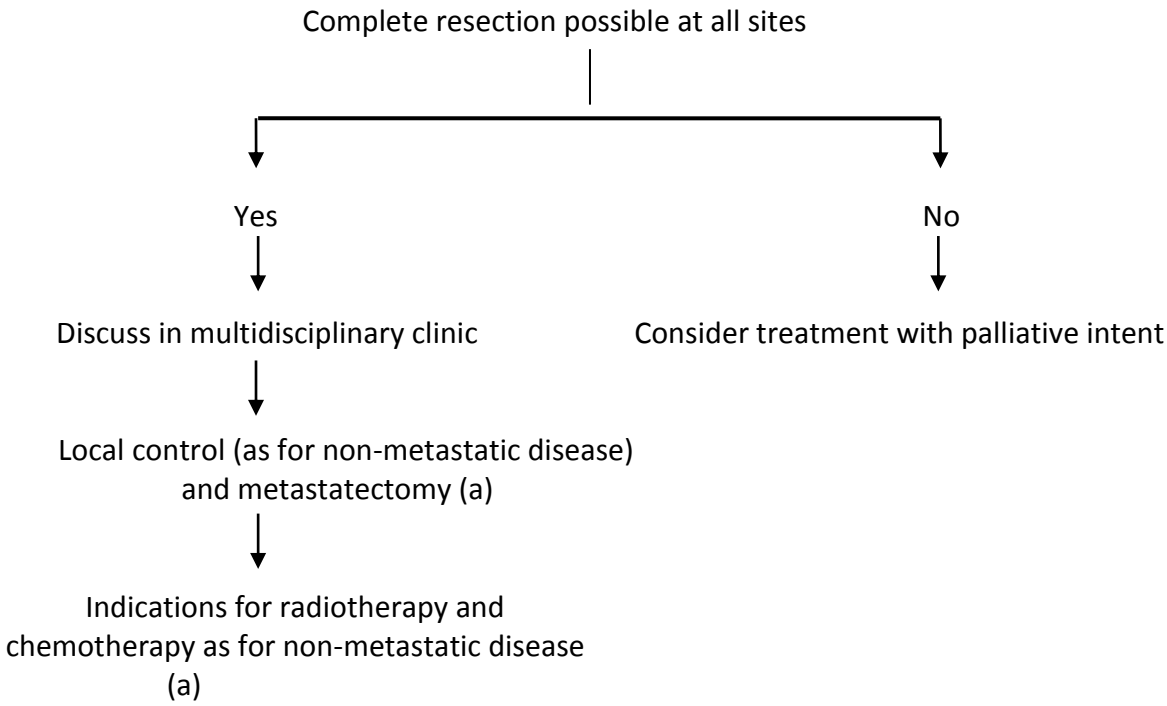
- All upfront resectable cases should be evaluated for feasibility of intra-operative interstitial brachytherapy.

Indications for post-operative radiotherapy (Appendix 6) (a)

- All high grade lesions
- All recurrent lesions
- Low grade lesions if deep seated /or ≥ 5cm /or margin close or positive

Chemotherapy may be offered to patients with high grade lesions > 5cm or recurrent lesions after discussion in multidisciplinary clinic.
Ifosfamide and doxorubicin combination is preferred (Appendix 5) (a)

EXTREMITY SOFT TISSUE SARCOMA – METASTATIC AT PRESENTATION



CHEMOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA

Regimen	Doses	Histology specific approval
Ifosfamide and doxorubicin	Ifosfamide(with mesna) 3 gm/m2/day for 3 days Doxorubicin 25mg/m2/day for 3 days with GCSF prophylaxis every 21 days	None
Single agent doxorubicin	75mg/m2 every 21 days	none
Pazopanib	800mg per day orally Administer on an empty stomach at least 1 hour before or 2 hours after a meal	Non adipocytic sarcoma
Trabectedin	1.5mg/m2 iv over 24 hours every 21 days (Premedicate with dexamethasone 20 mg to prevent hepatotoxicity)	Liposarcoma and leiomyosarcoma
Eribulin	1.4mg/m2 iv D1 and D8 every 21 days	Liposarcoma

- Decision for palliative intent of treatment should be taken after discussion in multi-disciplinary tumor board. The intent of treatment can change from palliative to curative or vice-versa based on the patient's clinical condition.

RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA

Adjuvant Radiotherapy (a)

Doses and technique -

1. Margin negative: 60Gy/30#s over 6 weeks with phased portals (Ph-1 50Gy/23#s followed by Ph-2 with shrinking portals 10Gy/5#s) (a)
2. Positive margin: To add a boost of 6-10Gy for microscopic/ gross positive margins to the above planned dose.
3. Brachytherapy dose: 36Gy/9#s @ 400cGy per dose, twice a day.

Preoperative radiotherapy ((c)to Adjuvant radiotherapy)

Doses and technique - 50Gy/25#s over 5 weeks (a)

Definitive Radiotherapy (c)

Doses up to 70Gy @ 1.8-2Gy/# to be considered

Palliative RT (c)

RT can be used for palliation of symptomatic sites (primary or metastatic or both) with dose fractionation depending upon tolerance and response.

SURVEILLANCE IN SARCOMAS

Follow up Strategy

During postoperative period patient attends rehabilitation services for physiotherapy

↓

Follow up every 6 months for the first 5 years (a)

Or

Every 3 months for first 2 years, every 6 months for next 3 years **(c)**

(Clinical evaluation, Radiological evaluation, Functional evaluation)

↓

Annual follow up after 5 years (a)

(Clinical evaluation, Radiological evaluation, Functional evaluation)

- **Clinical evaluation** - Examination of local area.
- **Radiological evaluation -** X-ray of the local part and Chest X-ray is done at every follow up. CT scan of chest may be considered every 6 months for first 2 years. **(c)**
- **Functional evaluation** - using special scores like MSTS Score etc.

APPENDIX – 1

Principles of management of sarcomas

General Principles:

Sarcomas are rare cancers that originate from transformed cells of mesenchymal origin. Sarcomas are connective tissue tumors and arise commonly from bones, muscles, tendons, cartilage, nerves, fat and blood vessels of the appendicular skeleton, but they can also arise from other areas of the body. There are more than 50 types of sarcomas and can be grouped into two main types a) Bone sarcomas and b) Soft tissue sarcomas (STS). Sarcomas account 12-15%& 1-2% of all cancers in the pediatric and adult population respectively. Outcomes for patients with sarcomas has improved significantly over the past 3 to 4 decades due to advances in diagnostic radiology, pathology, chemotherapy, radiation therapy, and improvement in surgical techniques including the availability of micro-vascular tissue transfers, improvements in prosthetic design and availability of bone auto-allografts.

Any suspicious lesion (see below) in the bone or soft tissue should be referred to a specialized sarcoma care unit for better outcomes.

When to suspect sarcoma:

a) BONE SARCOMA: Commonest presenting symptoms of bone sarcomas: non-mechanical pain and a palpable mass arising from bone. This needs evaluation by a biplanar plain radiograph. Features suggestive (but not diagnostic) of bone sarcoma are:
    - Bone destruction and/or pathological fracture
    - New bone formation
    - Periosteal reactions
    - Soft tissue mass
b) SOFT TISSUE SARCOMA: Any soft tissue lump greater than 5cmsand located deep to the deep fascia should be regarded as soft tissue sarcoma unless proved otherwise. Most STS present as painless progressive swelling.

Biopsy:

All patients with a suspected sarcoma must undergo complete local imaging (as per guidelines) before biopsy. Ideally, biopsies should be performed at the center where definitive treatment is planned, alternatively, it can be done by a clinician trained in performing biopsies and who understands the principles of limb salvage surgery. Core needle biopsy is the gold standard for most cases (a). Additional studies like immunohistochemistry, cytogenetic, and molecular studies are desirable in some sarcomas like Ewing's sarcoma and STS (c). A poorly performed biopsy may not only fail to provide the correct diagnosis but may lead the subsequent surgery being more extensive, thus making the limb salvage surgery difficult and can impact survival negatively.

Once the diagnosis of sarcoma has been established (Appendix 3/4), they should be treated at a specialized in sarcoma center by a multidisciplinary team (MDT).

Staging work up:

All malignant musculoskeletal tumors should undergo staging investigation to assess the extent of disease spread in the body. Imaging with radiographs in two perpendicular planes with MRI to evaluate local extent of the disease.

- Osteosarcoma and chondrosarcoma are staged with non-contrast CT scan (NCCT) of the chest and a bone scan. (a)
- Ewing' sarcoma requires bone marrow- aspiration & biopsy from two different sites in addition to NCCT chest and a bone scan. (a)
- **(c)**PET scan with a breath-hold CT scan of chest is an alternative and may obviate the need of invasive bone marrow biopsies.

- **STS Staging -** Local imaging to be performed prior to doing a biopsy (a). MRI with contrast is recommended in all cases (a). NCCT chest for metastatic workup is advised (a). Ultrasonography of regional lymph node basin may be done, particularly for angiosarcoma, synovial sarcoma, rhabdomyosarcoma, epithelioid sarcoma and clear cell sarcomas. (c)
- Additional imaging to be considered based on histology are as follows (a)

  i) MRI whole spine: Myxoid/round cell liposarcoma

ii) Contrast CT scan of abdomen and pelvis: Myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma, leiomyosarcoma.

iii) MRI brain: Alveolar soft part sarcoma and angiosarcoma

iv) Contrast CT scan of the Pelvis: Lower extremity well differentiated liposarcoma.

- The F18 FDG PET CT scan with a breath hold CT of the chest may be used for metastatic workup but is not cost effective and yet not recommended as standard of care **(c)**

Treatment:

Sarcomas are best treated by a multidisciplinary team comprising of a core team of musculoskeletal oncologist-surgeon, medical oncologist, radiation oncologist, radiologist and a pathologist. Cross consultations with other disciplines like thoracic surgery, GI surgery, plastic surgery, and rehabilitation medicine are essential to provide optimum oncological and functional outcomes. Treatment is planned as per guidelines and patients are reassessed periodically at different stages of treatment.

Further details: Sections on Osteosarcoma, Chondrosarcoma, Ewing's sarcoma and Soft tissue sarcoma

A.) SURGERY: Goal of surgery is to achieve adequate oncologic clearance with optimal function. Decision on type of surgical procedure is multifactorial and varies on case to case basis, depending on factors like patient's age, tumor site, size, extent, response to neo-adjuvant treatment, socio-economic factors, surgeon's expertise etc.

Resected specimens need to be evaluated for adequacy of surgical margins (Quantitative and Qualitative margins) and percentage necrosis (when neoadjuvant chemotherapy has been administered). (Appendix 3/4)

B.) CHEMOTHERAPY: Multiagent chemotherapy is the standard of care in osteosarcoma and Ewing's sarcoma**.** (Appendix 5). (a)

C.) RADIOTHERAPY: Osteosarcoma and chondrosarcoma are relatively radio-resistant tumors. Radiotherapy has a definite role in the management of Ewing's sarcoma and high-grade soft tissue sarcoma. (Appendix 6)

Surveillance:

Optimum surveillance is essential to diagnose local and/or distant relapse. A surveillance visit usually entails clinical and radiological examination. This helps to assess oncological and functional outcomes. Most recurrences occur in the first 2-3 years and decreases over time and these tumors are generally followed up to 10 years. Intense follow up may be required for first 5 years. Intensity of surveillance and interval between visits may vary based on risk stratification and Institutional protocols. Standard follow-up investigations include a detailed clinical history and examination, radiographs/ ultrasonography/ MRI of affected region with chest radiographs or CT scans. Visits are usually planned every 3 to 6 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter.

Principles of treatment

Bone Sarcomas:

- Baseline assessment of renal, cardiac and auditory function - (CBC, RFT, LFT, SE, ECHO, ECG, GFR, Audiomety.
- Counselling for Sperm banking for male patients of reproductive age while using ifosfamide.
- Fertility specialist consultation for female patients should be considered.
- Utmost care should be taken to avoid a pathological fracture; weight bearing precautions and splintage should be advised wherever deemed necessary. Presence of pathological fracture, either at presentation or during neoadjuvant chemotherapy may increase the risk of local and systemic recurrence and negatively impacts survival. Internal fixation of pathological fracture through a sarcoma should not be done; the limb should be splinted, and neoadjuvant chemotherapy started. Performance of limb can be attempted in a very carefully selected subset of these patients without increased risk of local recurrence or death, taking into account factors like histopathology, severity of fracture, degree of displacement, response to chemotherapy, fracture union and response to neo adjuvant chemotherapy. Ewing

sarcoma patients with pathological fractures require post-operative radiotherapy after limb salvage.

- All patients should be re-evaluated clinically before each cycle of chemotherapy Patients with disease progression during chemotherapy are at increased for local and systemic failure.

- Patients with disease progression during chemotherapy are at increased risk for local and systemic failure.

    - Local progression alone: Early definitive local therapy should be considered: May result in amputation.

    - Systemic progression during chemotherapy: These patients can be considered for best supportive care

- Adjuvant radiation where indicated should be advised. (Appendix 6)

- All patients considered for surgery should undergo evaluation with a contrast MRI, MRI should include entire length of the affected bone. Limb salvage surgery with wide margins and a functional limb is preferred.

- Type of local therapy (Amputation vs Limb Salvage Surgery) to be decided based on factors like local extent of tumor, involvement of adjacent structures, biopsy tracts, pathological fracture, any prior surgical procedures, vascular-nerve-soft tissue involvement, progression on chemotherapy etc.

- Type of limb salvage to be based on skeletal maturity, location of tumor (intercalary/trans-articular/extra-articular). Reconstructive techniques to be based on availability of resources and expertise.

- Plastic and vascular surgeons to be involved in surgical planning for reconstruction as indicated.

- In Ewing sarcoma, the decision on the choice of local therapy should follow an MDT discussion, and a detailed discussion with the patient/parents. Patients having metastases at presentation should have a systemic evaluation at the time of local therapy, in the form of a whole-body PET CT / NCCT chest as applicable. (a)

- Osteosarcoma metastatic at presentation (oligometastatic) and deemed treatable: Treatment practices as to the timing of surgery for primary and metastasis vary depending on a) institutional protocol and b) patient and disease factors.

- Management of recurrent Osteosarcoma needs to take into account the timing of recurrence / metastases, number of metastases, and site of metastases. Each case needs to be discussed in aMDT. (Appendix 5)

- Complete removal of all metastases must be attempted. No clear benefit of second line chemotherapy in isolated local recurrences. Patients with distant metastasis with more than 18-month DFI may be benefitted. These patients must be evaluated on case by case basis in multi-disciplinary team. (Appendix 5). Non operable metastases are treated with palliative intent treatment/ best supportive care.
- Oligometastatic Ewing's sarcoma (only pulmonary or isolated bone metastasis) at presentation is treated with curative intent. These patients are re-evaluated after induction chemotherapy with relation to local and systemic staging (a).
- Metastatectomy after completion of surgery of primary and all chemotherapy is an acceptable alternative (c).
- Lung bath is an essential component in the management of pulmonary metastasis in Ewing's sarcoma (a).
- Chondrosarcomas are radiotherapy resistant and chemotherapy resistant tumors, hence surgical excision remains the mainstay of treatment.

- Dedifferentiated chondrosarcomas may receive multi agent chemotherapy like high-grade Osteosarcoma (a).

- Mesenchymal chondrosarcoma may receive multiagent chemotherapy like Ewing's sarcoma (a).

- It may be safe to treat extremity grade I (low grade) chondrosarcomas with intra-lesional curettage without increasing the risk for local or metastatic recurrence.

- Osteosarcomas diagnosed as low grade on initial biopsy (parosteal / low grade intramedullary) are treated with wide excision only. If after definitive surgery a high-grade component is identified they receive multiagent adjuvant chemotherapy (a).

- Periosteal osteosarcomas are currently treated similar to high-grade osteosarcomas.

- For relapsed Ewing's Sarcoma, salvage therapy to be considered, if relapse occurs 12 months after completion of maintenance chemotherapy. Treatment of relapse should be decided in a MDT based on time of relapse, site(s) of relapse, prior treatment and performance status.

Soft Tissue Sarcoma:

- Type of local therapy (Amputation vs Limb Salvage Surgery) to be decided based on factors like local extent of tumor, involvement of adjacent structures, biopsy tracts, pathological fracture, any prior surgical procedures, vascular-nerve-soft tissue involvement, progression on chemotherapy.

- Plastic and vascular surgeons to be involved in surgical planning for reconstruction as indicated.

- The surgical specimen should be evaluated jointly by the surgeon and pathologist to evaluate margin status, preferably immediately after surgery.

- Radiation therapy should be considered for all high-grade tumours, tumours >5 cms, recurrent tumours and tumours with close/positive margins. Radiotherapy may be administered as intraoperative brachytherapy or external beam radiotherapy or a combination both (a). Radiotherapy may be delivered either as pre or postoperative radiotherapy depending on surgeon/institution preference. (Appendix 6)

- Currently there is inadequate evidence to recommend adjuvant chemotherapy as standard for all adult soft tissue sarcoma patients. It may be considered in a select population of high-grade extremity sarcoma, > 5 cm or recurrent high-grade tumours

using doxorubicin alone or a combination of doxorubicin plus ifosfamide after discussion in multidisciplinary clinic. Any potential benefits should be considered in the context of the short and long-term toxicities of chemotherapy. (Appendix 5)

- Management of metastatic STS, needs to take into account the timing of recurrence/metastases, number of metastases, and site of metastases. All cases should be discussed in MDT. Complete removal of all metastases must be attempted.
- Second line chemotherapy may be considered on case by case basis after discussion in MDT (c).

- Non-operable recurrences are treated with palliative intent treatment/ best supportive care.

- Palliative radiotherapy may be required for disease or pain control. Palliative chemotherapy/targeted therapy should be decided in a multidisciplinary clinic with careful selection of agents to have minimum side effect and better quality of life.

APPENDIX – 2

Imaging Evaluation of Bone and Soft Tissue Tumors

Imaging modalities include –

- Radiographs
- Magnetic Resonance Imaging (MRI)
- Computed Tomography (CT) Scan
- Bone scan
- Positron Emission Tomography (PET) / PET- CT

Radiograph:

Radiographs are easily available, inexpensive and are the first line of imaging in evaluation of the bone (a). Absolutely benign lesions on radiographs do not require additional work up, rest will require further imaging work up. Radiographs can be evaluated and in reported as per below reported format.

Radiographic approach to bone tumors

Radiograph quality - Acceptable / Not acceptable (whether/not joints proximal and distal to the lesion included in the lesion)

Age:

Skeletal maturity: Mature/immature

Location: Epiphysis/Metaphysis/Diaphysis/combination of these

Relationship to the bone: Central/eccentric/juxtacortical/juxtaarticular(does juxtaarticular lesion cross the joint)

Lesion type: Lytic/sclerotic; Dimensions:

Distance from nearest surgical landmark (distance from proximal and distal articular surface, landmarks like greater or lesser tronchanter):

Matrix: Osseous/Chondroid/Ground glass/indeterminate

If lytic, zone of transition: Narrow/Wide

Cortex: Intact/Expanded/Breached

Periosteum: Interrupted/uninterrupted

Uninterrupted Periosteal reaction: Solid/Unilaminar/Buttress

Interrupted periosteal reaction: Multilaminar (onion skin type)/Sunburst/Codman's triangle

In immature skeleton, relationship to physis: Uninvolved/crossed

Extraosseous soft tissue: Present/Absent

Number of lesion: Solitary lesion/polyostotic disease

Skip Lesions: Yes/no and their number/s

IMPRESSION: ……

Magnetic Resonance Imaging (MRI) :

Further evaluation of aggressive bone tumours will often require MR imaging (a)and is preferred over CT scan (c). The indications of doing MRI include further characterization of -

- Radiographically indeterminate lesion
- Aggressive bone lesions
- Normal radiograph with persistent localized symptoms.

MR imaging is superior in depiction of loco-regional anatomic detail, detecting marrow-based skip lesions apart from characterizing the bone lesions and generally preferred over CT and radionuclide studies, like bone and PET scan.

MRI can be evaluated and in reported as per below reported format.

Bone Tumor MRI Evaluation and Reporting Format

- History of previous therapy or intervention, if any
- Technique:
- Radiographic findings:
- Findings:

- Whether full bone is covered or not
- If Implant in situ - MARS protocol

- **PRIMARY TUMOR:**
- Location: Which bone and Epi/Meta/Dia; within bone: Intramedullary,

Juxtamedullary, Cortical, Juxta-Cortical
- Morphology: expansile/non-expansile, mention fluid-fluid levels
- Cortical Breach: present/absent
- Soft tissue component: present/absent.

- T2:hyper/iso/hypo
- T1: hyper/iso/hypo
- Diffusion restriction: present/absent
- PC Enhancement with/without dynamics: if Dynamic type of enhancement curve
- Measurement of the soft tissue: AP x TS x CC cm
- Craniocaudal extent of the marrow involvement: cm
- Distance from proximal joint or other major bony landmark: if applicable
- Distance from distal joint: if applicable
- Physeal plate involvement:
- Reaching upto articular surface:
- Joint Involvement:
- Presence of necrosis:
- Presence of haemorrhage:
- Presence of cystic areas:
- Neurovascular bundle Relationship:
- SKIP LESIONS AND OTHER LESIONS:
- Lymphadenopathy - Present / Absent, Local / Distant
- Other Incidental Findings:
- Comparison with prior study:

- Impression: …….

- MRI findings consistent/inconsistent with radiographic findings of_____
- Most likely diagnosis ± differential diagnosis

Computed Tomography :

CT scan has a limited value in diagnosis and evaluating the local extent of the disease. It is more useful in evaluation of distant spread of the disease like to lung and lymph nodes (a). The indications are -

- Staging for pulmonary metastasis in both bone and soft tissue sarcomas
- Diagnosing osteoid osteoma
- Patients with metallic implants
- Patients with contraindication to MRI

- Characterization of equivocal chondroid lesions
- Characterization of lesion on complex anatomical locations line vertebrae.
- Cortical involvement in some soft tissue lesions in close proximity with bone

Bone Scan:

Radionuclide bone scan do not aid diagnosis of bone tumours, however remains the primary imaging examination to screen for skeletal metastases (a). In pregnant patients instead of skeletal scintigraphy whole-body MR imaging can be done for the search of skeletal metastasis.

PET Scan:

PET scan is helping in staging sarcomas. FDG or F-18 PET scan are utilized. (c)

The indications are limited and would include:

- Staging and post-treatment evaluation of patients with osteosarcoma and Ewing sarcoma
- Identifying higher metabolic sites in negative biopsies for higher diagnostic yield
- Evaluation of patients with equivocal cartilage lesions in some settings
- Identifying areas of sarcomatous change in the borderline cartilaginous tumours.
- Evaluation of suspected metastatic bone disease myeloma or lymphoma.

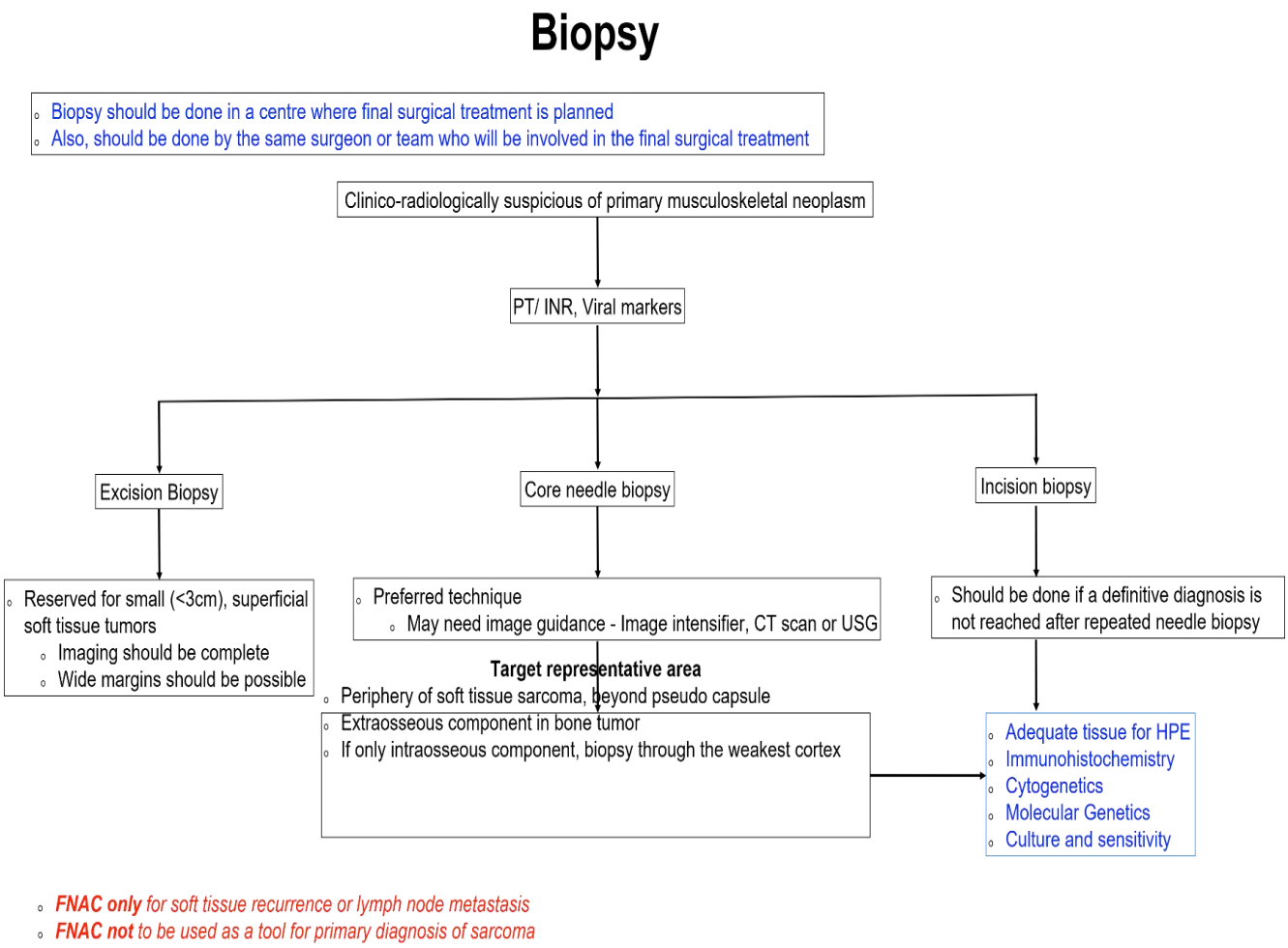
The use of FDG PET or PET/CT in the initial staging can lead to treatment optimisation particularly in Ewing's sarcoma patients due to the superiority of FDG PET in detecting bone lesions over a bone scan however in OGS patients, there is only little impact of FDG-PET on therapy planning because bone scan seems to be equally suited to detect skeletal involvement.

FDG PET/CT is useful in detecting recurrence at the primary site and is often complementary to other imaging modalities.

Like malignant lesions, infective pathologies and benign tumours can also show increased standard uptake values (SUVs), hence the reliability in differentiation is always a question, though it may be helpful in some cases.

Appendix - 3

Algorithm for performing biopsy in musculoskeletal lesions



- ***FNAC only*** *for soft tissue recurrence or lymph node metastasis*
- ***FNAC not*** *to be used as a tool for primary diagnosis of sarcoma*

APPENDIX – 4

Pathology Reporting formats

Bone Tumor Pathology Reporting Format

Name: ……Hospital no: ……Report no: ……

Grossed by: …… Reported by: ……

Consultant: ……

CLINICAL INFORMATION

Symptoms:

Duration of illness: Treatment history: or none

Others: Eg. H/o injury etc.

Exact Site: Location of Tumour: Type: Superficial / Deep. Clinical Tumour size:

Radiology findings

Bone involved:

Location of Tumor: Epiphysis/Metaphysis/Diaphysis

Superficial / Deep

Extent of lesion: Narrow zone/Wide zone

Type of lesion: Lytic/Sclerotic/ Mixed

Cortical destruction and Soft tissue involvement

GROSS DESCRIPTION

Type of Specimen: Core Needle biopsy, Curettage, Excisional biopsy, Amputation, Not specified.

Site: Epiphysis/apophysis, metaphysis, diaphysis (drop down); cortex, medulla, surface, joint, soft tissues, cannot be determined

Exact Tumor size: __x__x__(cm).

Gross margins (applicable in resection specimens). Anterior, posterior, superior, inferior, lateral, medial, Closest margin (unoriented resection):

HISTOLOGY

Histologic Subtype (According to WHO Classification of Bone Tumours):

_____

_____ ,

Mitotic count _____ per 10 hpf; Necrosis: present (less than 50%, 50% and more), absent.

Histological Grade (For Sarcoma): I, II, III. Low-grade, high-grade.

Lymphovascular invasion: present, absent.

Microscopic margins (in case of resection specimens)

Margin status cannot be ascertained.

Percentage necrosis (post chemotherapy treated resection specimens):

Less than 90 % (Poor), ≥ 90 %(Good) in cases of High-grade osteosarcoma and Ewing's sarcoma [c]

Lymph nodes if any: Involved……. Not involved…….

Skip lesions:

Metastasis: Nil/ Lung/Other sites

Ancillary Studies:

Recommended/ Not Recommended

Type of tests: (Interphase cytogenetics) FISH test *EWSR1*, etc.

Molecular by RT-PCR: *EWS-FLI1*, *EWS-ERG*, etc SYT-SSX, SYT-SSX1, SYT-SSX2, EWS-WT1, PAX3-FKHR, PAX7-FKHR.

TNM Tumour Stage: T/N/M (to type) / Cannot be ascertained.

Type of Resection: R0 / R1 / R2

Additional Comment: …….

Signature:

Registrar: **Consultant:** **Date:**

…….

TNM STAGING

Primary tumor (T):

Tx: Cannot be assessed

T0: No primary tumor

T1: ≤ 8cm, a: superficial b: deep

T2: > 8cm, a: superficial b: deep

Regional lymph nodes (N):

Nx: Cannot be assessed

N0: Negative

N1: Positive

Distant metastasis (M):

M0: No metastasis

M1: Distant metastasis

Stage IA	T1a N0,NX M0	Low grade
	T1b N0,NX M0	Low grade
Stage IB	T2a N0,NX M0	Low grade
	T2b N0,NX M0	Low grade
Stage IIA	T1a N0,NX M0	High grade
	T1b N0,NX M0	High grade
Stage IIB	T2a N0,NX M0	High grade

Soft Tissue Tumor Pathology Reporting Format

Name: ……Hospital no: …… Report no: ……

Grossed by:……Reported by:……Consultant:……

CLINICAL INFORMATION

Exact Site: Location of Tumour: Superficial / Deep: Clinical Tumour size:
Duration of illness: Treatment history:

GROSS DESCRIPTION

Type of Specimen: Needle core biopsy / Incisional biopsy / Excisional biopsy / Amputation

Exact Tumor size: __x__x__(cm).

HISTOLOGY

Histologic Subtype (According to WHO Classification of Soft Tissue Tumours):

_____
_____, exact type cannot be ascertained.
Mitotic count _____ per 10 hpf; Necrosis is seen (less than 50% / 50% and more) / not seen.
Histological Grade (For Sarcoma):
Lymphovascular invasion is seen / not seen / cannot be ascertained.
Microscopic margins _____
Margin status cannot be ascertained.
Ancillary Studies: Recommended/ Not Recommended _____
Cytogenetics (FISH test): Specify
Molecular (RT PCR): Specify
TNM Tumour Stage: / Cannot be ascertained.
Type of Resection: R0 / R1 / R2
Additional Comment: ……_
Signature:
Registrar: Consultant: Date:
……
……

TNM STAGING

Primary tumor (T):
Tx : Cannot be assessed
T0 : No primary tumor
T1 : ≤ 5cm, a: superficial b: deep
T2 : > 5cm, a: superficial b: deep
Regional lymph nodes (N):
Nx : Cannot be assessed
N0 : Negative
N1 : Positive
Distant metastasis (M):
M0: No metastasis
M1: Distant metastasis

Tumour site:
Superficial: Defined as above fascia. This includes dermal and subcutaneous
Deep: Defined as below fascia. This includes Fascial, Subfascial, Intramuscular, Mediastinal, Intra-abdominal, including Retroperitoneal, Head and Neck.

Histologic Grading:
System used: French Federation of Cancer Centres Sarcoma Group (FNCLCC)
Grade 1 (Total Scores = 2-3), Grade 2 (Scores 4-5), Grade 3 (Scores 6-8)
(i) Tumor Differentiation Score: (1-3):
Well-differentiated liposarcoma
1
Myxoid liposarcoma
2
Round cell liposarcoma
3
Pleomorphic liposarcoma
3
Dedifferentiated liposarcoma
3
Fibrosarcoma
2
Myxofibrosarcoma (malignant fibrous histiocytoma [MFH])
2
Storiform MFH (sarcoma, not otherwise specified [NOS)]
3
MFH, pleomorphic type (patternless pleomorphic sarcoma)
3
Giant cell and inflammatory MFH (pleomorphic sarcoma, NOS, with giant cells or inflammatory cell) 3
Well-differentiated leiomyosarcoma
1
Conventional leiomyosarcoma
2
Poorly differentiated / pleomorphic / epithelioid leiomyosarcoma
3
Biphasic / monophasic synovial sarcoma
3
Poorly differentiated synovial sarcoma
3
Pleomorphic rhabdomyosarcoma
3
Mesenchymal chondrosarcoma
3
Extra-skeletal osteosarcoma
3
Ewing's sarcoma / Primitive neuroectodermal tumor
3
Malignant rhabdoid tumor
3

Undifferentiated sarcoma
3

(ii) Mitosis (Score): (1-3)
0-9/10 high power field (hpf) =1, 10-19/10 hpf =2, ≥ 20/10hpf =3
(iii) Necrosis (Percentage) (Score): (0-2)
Defined as coagulative tumor necrosis in untreated specimens (chemo or radio)
0 = No necrosis, 1= <50% tumor necrosis, 2=> 50% tumor necrosis
Grade 1 = Low Grade. Grades 2 and 3 = High Grade.

Stage IA	T1a N0,NX M0	Low grade
	T1b N0,NX M0	Low grade
Stage IB	T2a N0,NX M0	Low grade
	T2b N0,NX M0	Low grade
Stage IIA	T1a N0,NX M0	High grade
	T1b N0,NX M0	High grade
Stage IIB	T2a N0,NX M0	High grade
Stage III	T2b N0,NX M0	High grade
Stage IV	Any T N1 M0	Any grade
	Any T Any N M1	Any grade

APPENDIX - 5

Chemotherapy for Bone and Soft Tissue Tumors

Bone Sarcoma

Background

Chemotherapy is an important component of the management of bone tumors. Chemotherapy can be given with curative intent or used in the palliative setting for symptom control. The choice of chemotherapy regimen will depend on the tumor histology, disease stage, patient's performance status, organ function, available infrastructure, and associated comorbidities.

Pre-requisites before administration of chemotherapy.

It is important to clinically examine the patient and perform laboratory tests before the administration of chemotherapy. The chemotherapy should be administered under the supervision of a qualified medical oncologist. All cases should be discussed in the multidisciplinary tumor board including a surgical oncologist and radiation oncologist before starting treatment.

Regimen for Osteosarcoma

First-line treatment:

The following regimens are commonly used in the neoadjuvant, adjuvant and palliative setting (a)

1. Cisplatin and doxorubicin (cisplatin and doxorubicin)
2. Ifosfamide, doxorubicin and cisplatin (IAP regimen)
3. Methotrexate, doxorubicin and cisplatin regimen (MAP)

It is important to ensure adequate intravenous hydration in patients receiving chemotherapy for osteosarcoma as cisplatin and methotrexate are nephrotoxic.

Regimen [reference}	Schedule
Cisplatin + doxorubicin	Days 1–3: Doxorubicin 25mg/m^2/day IV over 2 hours, plus Day 1: Cisplatin 100mg/m^2 IV over 3 hours Repeat cycle every 3 weeks for 6 cycles.
MAP (high-dose methotrexate + cisplatin + doxorubicin)	**Neoadjuvant (week 1-10/2 cycles)** Cisplatin 120 mg/m² (4 h infusion of 60 mg/m² per day for 2 days) and doxorubicin 37·5 mg/m² per day on days 1 and 2 as 4-hour infusion (on weeks 1 and 6). This is followed by high-dose methotrexate 12 g/m² over 4 h (maximum dose 20 gm)

	with hyper-hydration, alkalinisation, and standard leucovorin rescue at a dose of 15 mg/m² starting 24–48 h from methotrexate infusion and continuing until methotrexate concentration was less than 0·1 µM (weeks 4, 5, 9, and 10). **Surgery: week 11** **Adjuvant chemotherapy (week 12-29/4 cycles)** Cisplatin 120 mg/m² (4 h infusion of 60 mg/m² per day for 2 days) (on week 12 and 17). Cisplatin is capped at a cumulative dose of 480 mg/m² Doxorubicin 37·5 mg/m² per day on days 1 and 2 as 4-hour infusion (on week 12, 17, 22 and 26). High-dose methotrexate 12 g/m² over 4 h (maximum dose 20 gm) with hyper-hydration, alkalinisation, and standard leucovorin rescue at a dose of 15 mg/m² starting 24–48 h from methotrexate infusion and continuing until methotrexate concentration was less than 0·1 µM (weeks 15, 16, 20, 21, 24, 25, 28, 29). **Note:** Pegfilgrastim 6 mg is given on the day after completing doxorubicin infusion. Patients treated with amputation restart chemotherapy 3 to 5 days after surgery; patients who undergo limb salvage or rotation plasty restart chemotherapy 10 to 21 days after surgery.
Ifosfamide, Adriamycin and Cisplatin (IAP)	Ifosfamide 1.3 gm/m² day 1,2 and 3 Adrimaycin 50 mg/m² day 1 Cisplatin 100 mg/m² divided over day 1-3

- The treating medical oncologist will decide on the dose and schedule based on the patient's needs. The above regimens are for guidance purposes only.
- The above regimens are also used in patients with metastatic disease.
- All the above regimens require growth factor support and routine monitoring of hemogram and biochemical parameters as per institutional policy.

Salvage/Second-line chemotherapy

Second-line chemotherapy for patients with relapsed/refractory disease is given below (a). There is evidence from retrospective studies that multi-agent chemotherapy is associated with better survival than with single-agent chemotherapy. Patients who relapse within 12 months to 18 months of completion of treatment don't respond well to chemotherapy.

Regimen	**Schedule**
Gemcitabine + docetaxel	Days 1 and 8: Gemcitabine 675mg/m² IV, plus Day 8: Docetaxel 75–100mg/m² IV.

	Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).
Carboplatin + ifosfamide + etoposide	Days 1 and 2: Carboplatin 400mg/m^2/day IV, plus Days 1–5: Ifosfamide 1,800mg/m^2/day IV + mesna + etoposide 100mg/m^2/day IV. Repeat cycle every 3 weeks for up to 12 cycles
Cyclophosphamide + topotecan	Days 1–5: Cyclophosphamide 250mg/m^2 IV over 30 minutes Days 1–5: Topotecan 0.75mg/m^2 IV over 30 minutes Repeat cycle every 3 weeks for 12–14 cycles.
Ifosfamide (high dose) ± etoposide	Days 1–5: Ifosfamide 1,800mg/m^2/day IV + mesna, plus Days 1–5: Etoposide 100mg/m^2/day IV. Repeat every 3 weeks for 12 cycles.

- Not in order of preference. The treating medical oncologist will decide on the dose and schedule based on the patient's needs. The above regimens are for guidance purposes only.
- Any drug which was/ were not used in first-line settings can be used in a second-line setting.

Chemotherapy for Ewing's Sarcoma

First-line non-metastatic disease (Neoadjuvant/Adjuvant) (a)

Regimen [reference]	**Schedule**
VAC/IE (vincristine + doxorubicin + cyclophosphamide alternating with ifosfamide + etoposide)	**Alternating VAC and IE cycles** *VAC cycles* **Day 1:** Vincristine 2 mg/m^2 (max 2mg) IV over 5-10 minutes **Day 1:** Doxorubicin 75mg/m^2 IVP or Dactinomycin 1250mcg/m^2 IVP (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m^2 has been met) **Day 1:** Cyclophosphamide 1200mg/m^2 IV over 60 minutes + Mesna *IE cycles* **Days 1-5:** Ifosfamide 1800 mg/m^2 IV over 3 hours + Mesna **Days 1-5:** Etoposide 100mg/m^2 IV over 60 minutes Repeat each cycle every 2 weeks or 3 weeks for 17 cycles
VIDE (vincristine +	**Day 1:** Vincristine 1.5 mg/m^2 (max 2mg) IV push over 5-10

ifosfamide + doxorubicin + etoposide)	minutes **Days 1-3:** Ifosfamide 3g/mg^2 IV continuous infusion over 1-3 hours + Mesna (give concurrently with ifosfamide) **Days 1-3:** Doxorubicin 20mg/m^2 IV continuous infusion over 4 hours or Dactinomycin 500mcg/m^2 IV (Substitute for doxorubicin when cumulative lifetime doxorubicin dose of 375mg/m^2 has been met) **Days 1-3:** Etoposide 150mg/m^2 IV over 1 hour Repeat cycle every 3 weeks for up to 6 cycles

First-line treatment metastatic disease

Patients receiving treatment with palliative intent can be given VAC every 3 weeks up to 6-12 cycles. Patients receiving treatment with curative intent can be treated with VAC/IE as for non-metastatic disease. (a)

Second-line treatment for relapsed/refractory disease (a)

Regimen [reference]	**Schedule**
Cyclophosphamide + topotecan	Days 1–5: Cyclophosphamide 250mg/m^2 IV over 30 minutes Days 1–5: Topotecan 0.75mg/m^2 IV over 30 minutes Repeat cycle every 3 weeks for 12-14 cycles
Irinotecan ± temozolomide	Days 1–5: Temozolomide 100mg/m^2/day orally, plus Days 1–5 and 8–12: Irinotecan 10–20mg/m^2/day IV at least 1 hour after temozolomide. Repeat cycle every 3 or 4 weeks.
Docetaxel + gemcitabine	Days 1 and 8: Gemcitabine 675mg/m^2 IV, plus Day 8: Docetaxel 75–100mg/m^2 IV. Repeat cycle every 3 weeks for up to 13 cycles (median 4 cycles).

Note: not in order of preference

Soft Tissue Sarcoma

Available evidence from meta-analysis and randomized controlled trials suggests that adjuvant chemotherapy improves relapse free survival, data on overall survival however is conflicting.

Modalities of delivering chemotherapy

Neoadjuvant chemotherapy - NACT can be given in borderline resectable tumors with chemo sensitive histologies. It may help to shrink the tumor and may increase resectability. The responses are unpredictable. This may be combined with preoperative RT but toxicities are higher. All such cases should be discussed in MDJC and patient selection should be done carefully.

Adjuvant chemotherapy – Adjuvant chemotherapy should be considered in STS post-surgery if it is >5cm and high grade and deep seated in chemo-sensitive histologies like leiomyosarcoma, synovial sarcoma, myxoid liposarcoma, myxofibrosarcoma, pleomophic undifferentiated sarcoma and can be avoided in histologies like clear cell sarcoma, alveolar soft part sarcoma. However, in fewer histologies like MPNST, epitheloid sarcoma it can be done on case to case basis in MDT. Data from most trials recommend 5-6 cycles of adjuvant chemotherapy (a).

Advanced, Unresectable or Metastatic Disease.

First Line - Single agent chemotherapy (doxorubicin, ifosfamide, dacarbazine, epirubicin) or doxorubicin-based combination chemotherapy (with dacarbazine/ifosfamide) have been wide used for advanced, unresectable or metastatic STS. Other agents like gemcitabine, docetaxol, vilnorebine and temozolamide have also been evaluated in clinical trials. Single agent chemotherapy may be considered for other patients to avoid toxicity. (a)

After failure of the second-line therapy, best supportive care should be considered, particularly in patients with non-leiomyosarcoma histology.

Second Line Therapy**– (c)**

Second line therapy after first line therapy favours histology directed approach.

Pazopanib, Trabectedin and Eribulin are mainly used agents. Other drugs used as second line therapy - paclitaxel for angiosarcoma, propanolol for angiosarcoma, sorafenib for desmoid tumors and Tazemetostat for INI negative epitheloid sarcoma. Similarly, ALK inhibitors like crizotinib are effective in ALK positive IMFT and various anti angiogenic agents like sunitinib are effective in advanced ASPS.

Summary of drugs and doses in localized and advanced STS

Regimen	Doses	Histology specific approval
Ifosfamide and doxorubicin	Ifosfamide(with mesna) 9 gm/m2 Doxorubicin 75mg/m2 Divided over 3 or 5 days with GCSF prophylaxis every 21 days	None
Single agent doxorubicin	75mg/m2 every 21 days	none
Pazopanib	800mg per day orally Administer on an empty stomach at least 1 hour before or 2 hours after a meal	Non adipocytic sarcoma
Trabectedin	1.5mg/m2 iv over 24 hours every 21 days (Premedicate with dexamethasone 20 mg to prevent hepatotoxicity)	Liposarcoma and leiomyosarcoma
Eribulin	1.4mg/m2 iv D1 and D8 every 21 days	Liposarcoma

APPENDIX - 6

Radiotherapy for Bone and Soft Tissue Tumors

Bone Sarcomas

Ewing's Sarcoma -

Adjuvant Radiotherapy (a)

Radiotherapy doses and technique

3. Margin negative R0 resection: 45Gy/25#s over 5 weeks (a)
4. Positive margin: R1 resection - 50.4Gy/28#s over 6 weeks, R2 resection - 55.8Gy/31#s over 6.5 weeks (a).
5. Target volumes should encompass the tumor bed along with margins for the microscopic disease. Scar and the drain site need not be chased. Tailored portals for all patients (a). IMRT +/- IGRT can be used (c).

Definitive Radiotherapy (c)

RT is preferred over surgery as local treatment for tumors presenting with metastatic disease (RT for primary as well as metastatic sites)

Radiotherapy doses and technique

1. 55.8Gy/31#s over 6 weeks (a)
2. Target volumes should encompass the gross tumor (GTV) with margin for microscopic disease (CTV).
3. Tailored portals for all patients (a). IMRT +/- IGRT can be used (c).
4. Adaptive RT may be considered if required (c).
5. Concurrent CTRT protocol to be used while on RT.

Lung bath (a)

The recommended dose for lung bath is 12.6Gy/7#s over 10 days with tailored portals (a).

RT in metastatic disease

RT may be preferred local treatment (for primary as well as the metastatic sites) in oligometastatic cases (c). RT doses are same as that of non-metastatic cases. Hypofractionated RT can be considered for skeletal metastatic sites.

Patients with disseminated disease or with multiple bony metastasis should be treated with palliative intent **(c).**

Palliative RT

RT can be used for palliation of symptomatic sites (primary or metastatic or both) with dose fractionation depending upon tolerance and response (c).

Osteosarcoma and Chondrosarcoma -

Radiotherapy doses and technique

1. Definitive RT up to doses of ≥70Gy@ 1.8-2Gy/# to be considered (a).
2. Conformal portals, adaptive planning and image guidance is recommended (a).
3. Select cases to be considered for particle beam therapy (c).

Soft Tissue Sarcomas

Radiotherapy reduces local recurrences and may have an impact on the overall survival in STS. Intra operative interstitial brachytherapy should be considered for extremity STS, wherever feasible.

Adjuvant Radiotherapy (a)

Indications of adjuvant RT

1. High grade tumors
2. Tumors>/= 5 cms
3. Close or positive margins
4. Recurrent tumors

Radiotherapy doses and technique

4. Margin negative: 60Gy/30#s over 6 weeks with phased portals (Ph-1 50Gy/23#s followed by Ph-2 with shrinking portals 10Gy/5#s) (a)
5. Positive margin: To add a boost of 6-10Gy for microscopic/ gross positive margins to the above planned dose.
6. Target volumes should encompass the tumor bed along with margins for the microscopic disease. Scar and the drain site need not be chased. Tailored portals for all patients (a). IMRT +/- IGRT can be used (c).
7. Attempt should be made to spare around 1.5 - 2.0cm of limb circumference as well as reduce doses to uninvolved bone/ joint and minimize hotspots on the skin and subcutaneous tissues (a).
8. Radio-opaque clips placed during surgery help in defining the tumor bed. (c)
9. Adjuvant chemotherapy if planned, to be considered after completion of RT.
10. Brachytherapy dose: 36Gy/9#s @ 400cGy per dose, twice a day.

Preoperative radiotherapy ((c)to Adjuvant radiotherapy)

To be considered for marginally/borderline resectable cases.
Radiotherapy doses and technique

1. 50Gy/25#s over 5 weeks (a)
2. Target volumes should encompass the tumor (GTV) with a 2cms margin for microscopic disease (CTV).
3. Tailored portals for all patients (a). IMRT +/- IGRT can be used (c).
4. Adaptive RT may be considered if required (c).
5. Neo-adjuvant chemotherapy if planned, to be considered either before starting RT or after completion of RT.

Definitive Radiotherapy (c)

To be considered for select cases with unresectable/ inoperable tumors.

Doses up to 70Gy @ 1.8-2Gy/# to be considered. Conformal portals, adaptive planning and image guidance can be considered.

Palliative RT (c)

RT can be used for palliation of symptomatic sites (primary or metastatic or both) with dose fractionation depending upon tolerance and response. They may help decreasing pain, temporarily arresting tumor growth or to achieve haemostasis.