Extremity Soft Tissue Sarcoma

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Supriya Mallick and Goura K. Rath

Soft-tissue sarcomas are relatively uncommon cancers accounting for less than 1% of all new cancer cases. It includes a wide variety of histological subtypes with variable chemosensitivity and radiosensitivity

38.1 Risk Factors

Only few environmental risk factors have been associated with the development of soft tissue sarcoma:

- Chlorophenols in wood preservatives and phenoxy herbicides
- Vinyl chloride increased risk of angiosarcoma
- Human herpes virus 8 has been implicated in the development of Kaposi's sarcoma

38.2 History Taking

- Swelling
- Pain
- Change in color
- Any history of trauma

38.3 Examination

- Start with examination of the swelling
- Site, number
- Size
- Shape—spherical, oval, irregular
- Surface and skin over swelling—color, punctum, inflammation, scars over swelling—recurrence, dilated veins
- Borders/edge—well defined and regular
- Consistency—soft, cystic, firm, hard
- Pulsations
- Palpation—tender/local rise of temperature—first to do in palpation
- Fixity—skin and deeper structures—pinch skin over swelling, move in direction and perpendicular to fibers
- Location—contraction of muscle
  - Superficial remains mobile and become prominent
  - Muscular—becomes immobile and fixed
  - Deep to muscle it becomes less palpable—look at draining LN
- Distal pressure effects in limb swelling
  - Distal wasting of muscles, movements and power of distal muscles, sensations—for nerve compression
  - Distal pulsations—for arterial occlusion
  - Distal effects including edema—pressure effects and dilated veins—for venous occlusion

S. Mallick (✉) · G. K. Rath
Department of Radiation Oncology, National Cancer Institute-India (NCI-India), Jhajjar, Haryana, India

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- Examination of lymph nodal region adjacent to the swelling
  - Particularly in: RMS, angiosarcoma, clear cell sarcoma
- Abdominal examination—rarely hepatomegaly or PA LN
- Respiratory—lung metastasis is common
- CVS and CNS examination

38.4 Differential Diagnosis

- Benign soft tissue mass
- Metastasis
- Organized hematoma

38.5 Workup

- Complete blood counts, RFT, LFT
- Biopsy: Direction should be parallel to the tumor, planned in such a way that the biopsy pathway and the scar can be safely removed by definitive surgery
- FNAC: Advised in few cases
- MRI—local part, preferred except in retroperitoneal and thoracic tumors where CT may be sufficient
- CECT Chest
- CT scan abdomen/pelvis—in patients with myxoid/round cell liposarcoma and leiomyosarcoma

38.6 Staging: FIGO—Clinical Staging

The factors that are taken into account for the TNM staging of soft tissue sarcomas are tumor size, nodal status, grade (differentiation score), and metastasis.

The AJCC 08 TNM staging for extremity soft tissue sarcoma is summarized in Table 38.1.

Three-tier system is commonly used for grading. The FNCLCC (French) system is the preferred grading system (Table 38.2).

Table 38.1 AJCC08 TNM staging for extremity soft tissue sarcoma

T staging	N staging	Stage grouping
T1—Size less than or equal to 5 cm T2—Size greater than 5 cm < 10 cm T3—5–10 cm size T4—Size more than 15 cm	N0—No N1—Yes *M staging* M0—None M1—Yes	• IA—T1 N0 M0 G1 • IB—T2-4 N0 M0 G1 • II—T1N0 M0 G2-3 • IIIA—T2 N0 M0 G2-3 • IIIB—T3-4 N0 M0 G2-3 • IV—N1/M1

Table 38.2 French Federation of Cancer Centers Sarcoma Group grading

Tumor differentiation	Mitotic count	Tumor necrosis	Grade
1 point: resembles normal adult mesenchymal tissue 2 points: histologic typing is certain 3 points: synovial sarcoma, osteosarcoma, Ewing's sarcoma, etc.	1 point: 0–9 mitoses 2 points: 10–19 mitoses 3 points: 20 or more mitoses	0 points: no necrosis 1 point: <50% necrosis 2 points: >50% necrosis	Grade 1: Total 2–3 points Grade 2: 4–5 points Grade 3: 6–8 points

38.6.1 Patterns of Spread

- Distant metastases—most common pattern of spread
  - 10% have distant metastasis at presentation
  - Lung is the most common site (70–80%) of spread of extremity sarcomas
  - 80% of distant metastasis appear within 2 years
- Lymph nodes—Less common than distant metastasis
  - Only 5% of the patients with sarcomas have positive lymph nodes at presentation
  - Increased risk of lymph node metastasis occurs in synovial sarcoma (14%), clear cell sarcoma (28%), angiosarcoma (23%), rhabdomyosarcoma (15%), and epithelioid sarcoma (20%) (SCARE)

Risk of Distant Metastasis *Depends on Grade*, tumor size, depth, and neurovascular bone involvement are independent predictors of metastasis.

38.6.2 Prognostic Factors

38.6.2.1 Increased Risk for Local Recurrence

- Age >50
- Recurrent disease
- Positive surgical margins
- Fibro sarcoma (including desmoid)
- Malignant peripheral nerve tumors

38.6.2.2 Increased Risk of Distant Metastasis

- Size >5 cm
- High grade
- Deep location
- Recurrent disease
- Leiomyosarcoma

38.6.3 Treatment Overview

Surgery Historically amputation was the treatment of choice for extremity, then full compartment resection. At present en-bloc resection with 2 cm margin considered standard. Resection of skin and bone rarely required.

38.6.3.1 Approaches

1. Amputation vs. limb-sparing surgery + post-op chemo-RT
   - *National Cancer Institute* randomized 43 patients with high-grade soft tissue sarcomas of the extremities, without distant metastasis to either amputation vs. limb-sparing surgery + post-op chemo-RT [1]
   - *Radiation dose*: 45–50 Gy followed by a boost to 60–70 Gy
   - All patients received post-op chemotherapy
   - Outcome: Local failure limb-sparing 15% vs. amputation 0% ($p = 0.06$)
   - 5-year DFS 71% vs. 78% (NS)
   - 5-year OS 83% vs. 88% (NS)
2. Surgery + post-op EBRT vs. surgery alone
   - *National Cancer Institute* randomized patients with extremity to either limb-sparing surgery followed by adjuvant radiation of 63 Gy with concurrent chemotherapy or chemotherapy alone [2]
     - High grade: local recurrence chemo-RT 0% vs. chemo 19%
     - 10-year OS 75% vs. 74% (NS)
     - Low grade tumors: local recurrence RT 4% vs. observation 33% (SS)
     - It reflected that adjuvant RT is highly effective in preventing local recurrence
3. Preoperative radiotherapy

   Trials on pre-operative radiotherapy are summarized in Table 38.3
4. Preoperative RT vs. adjuvant RT

   O'Sullivan et al. from NCI Canada performed a randomized trial comparing pre-op RT vs. post-op RT which included 190 patients. Primary endpoint was a major wound complication. The pre-op RT group received 50 Gy in 25 fractions with an option of additional 16–20 Gy post-op boost. The post-op RT arm received a dose of 66–70 Gy. Initial radiotherapy field included 5 cm proximal/distal margin followed by the boost which included 2 cm proximal/distal margin. Longitudinal strip of skin was untreated for at

Table 38.3 Trials on pre-operative radiotherapy

Trial	Number	Inclusion criteria	Arms	outcome
RTOG 95–14 [3]	64	Large (≥8 cm), high grade (G2-3) expected R0 resection	Neoadjuvant sequential chemo-RT	3-year LRF 18% 3-year DFS 57% Toxicity-high
DeLaney et al. [4]	48	Large (≥8 cm), high grade (G2-3)	Neoadjuvant sequential chemo-RT	5-year LC 92% DFS 75% OS 44%

least half the course to avoid lymphedema. Acute wound complications worsened after pre-op RT but long-term extremity function worsened after adjuvant RT [5].

Al-Absi et al. performed a meta-analysis of 5 studies with 1098 patients and found that local recurrence was better in pre-op group (HR 0.6, SS). Survival pre-op group was 76% vs. 67% in the post-op RT cohort [6].

38.7 Radiotherapy Planning for Soft Tissue Sarcoma

38.7.1 Indications for RT

- RT for all tumors >5 cm and deep
- High grade even if ≤5 cm and deep
- If the surgical margin was less than 10 mm

38.7.2 PORT Dose

- 66–70 Gy in 2 Gy per fraction depending on margin status

38.7.3 Volumes

- 2 Phase plan
  - Phase 1 CTV for limbs—operative bed plus 5 cm longitudinal and 2 cm radial margin and includes the scar and biopsy sites
  - Phase 2 CTV has only a 2 cm longitudinal margin
  - A 2D plan for extremity soft tissue sarcoma is shown in Fig. 38.1
  - Spare a strip of skin to avoid long-term lymphedema

Target volume according to VORTEX trial: 2 cm cranio-caudal margin to GTV and minimum margin of 2 cm axially forms the CTV 1 cm margin for PTV, treatment in single phase (no Boost)

VORTEX trial was aimed to look into the feasibility of reducing volume of tissue irradiated

Control arm (C): 50 Gy in 25 fractions to CTV1 (GTV + 5 cm cranio-caudally and 2 cm axially) followed by 16 Gy in 8 fractions to CTV2 (GTV + 2 cm cranio-caudally and axially) or the Experimental arm (R): 66 Gy in 33 fractions to CTV2 alone. Two hundred sixteen patients were randomized. The initial results show 5-year local recurrence free survival (LRFS) rates were 86% vs. 84%. 5-year overall survival was 72% vs. 67%.

Brachytherapy for Soft Tissue Sarcoma
Described in brachytherapy chapter.

38.8 Chemotherapy

38.8.1 Adjuvant

- The definite role of adjuvant chemotherapy is not proven beyond doubt—Maybe considered for high-risk patients—high-grade tumors, deep, >5 cm tumor, after discussing with patients potential toxicity and benefits
- Ifosfamide and adriamycin chemotherapy

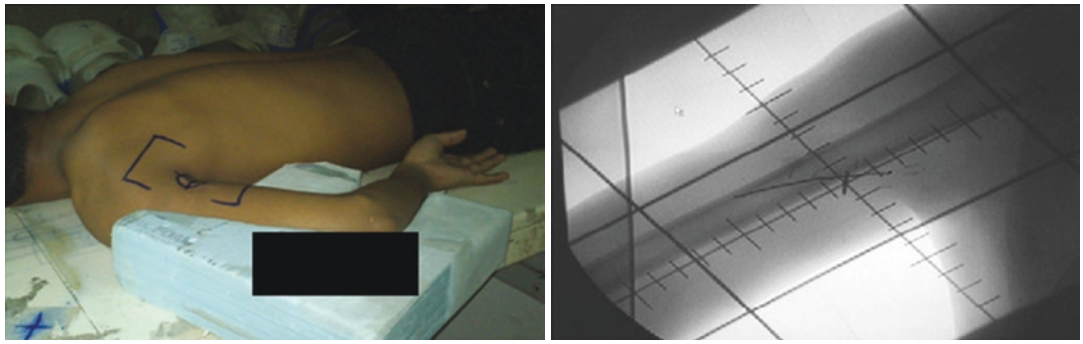

Fig. 38.1 2D planning in a patient with limb sarcoma

38.8.2 Metastatic

- Maybe useful in metastatic setting—histology driven chemotherapy
- Relatively chemoresistant
- If limited lung metastasis—may be considered for resection
- Single agent anthracyclines are preferred first line agent
- Only agent proved beneficial in combination with anthracycline-olaratumab (blocks PDGF-AA and PDGF-BB from binding PDGFRα) has OS benefit
- Other agents
  - Myxoid/round cell liposarcoma—trabectedin
  - Undifferentiated pleomorphic sarcomas—gemcitabine and docetaxel
  - Pazopanib—advanced *non*-adipocytic STS
  - Sunitinib—alveolar soft-part sarcomas and solitary fibrous tumor
  - Angio sarcoma—taxanes may be beneficial
  - Eribulin—liposarcoma

38.9 Follow-Up

- History and physical examination with X-ray or CT chest every 3–6 months in first 2–3 years
- Then every 6 months till 5 years and then annually

Source of Image Image have been taken from patient treated by author and consent have been taken.

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