Soft Tissue Sarcoma

Approach to a patient

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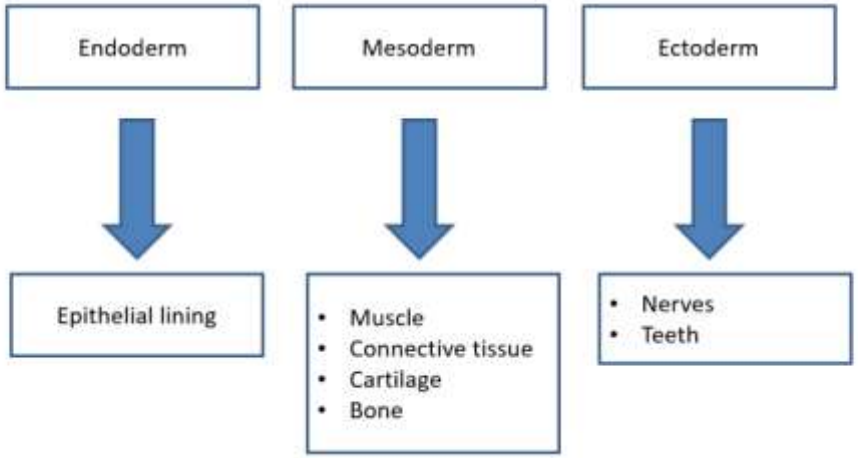
If You're Not Confused,
You're Not Paying Attention.

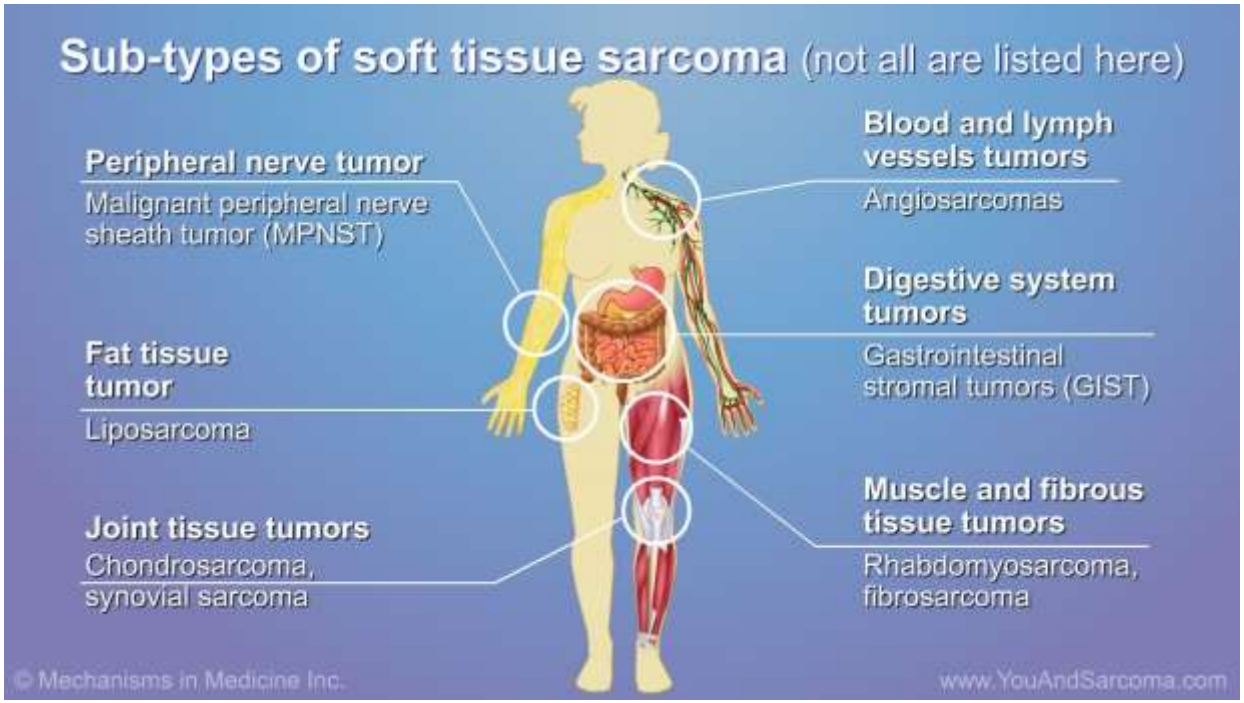
- Soft tissue is defined as non-epithelial extra skeletal mesenchyme exclusive of reticulo-endothelial system and glia
- Most of the soft tissues derived from mesoderm with neuro-ectodermal contribution corresponding to peripheral nerve.

Origin of sarcomas



- Soft tissue sarcoma
- Bone sarcoma
- Sarcomas of childhood
- Others (GIST and Kaposi's)

- Soft tissue sarcomas (STS) constitute a group of rare malignancies that vary extensively by anatomic location, histology, and biologic behavior.



- They can occur at any anatomic site and may arise from many soft tissues including connective tissues, fat, muscle, vascular tissue, peripheral neural tissue, or visceral tissue

- STS accounts for <**1%** of overall malignant tumors, **1%** of **adult** & **7-15 %** of **pediatric** malignancies

Pathology

- The WHO divides soft tissue tumors into 4 categories:
  - **Benign**;
  - **Intermediate, locally aggressive** (e.g desmoid fibromatosis)
  - **Intermediate, rarely metastasizing** (e.g plexiform fibrohistiocytic)
  - **Malignant**

- There are more than **50** histologic subtypes of STS

- The most common subtypes include ***undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, myxofibrosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor***.

- These account for about **75%** of STS cases

Brady & perez

Natural History

- STS tends to invade longitudinally along **musculoaponeurotic** planes
- Rarely cross fascial boundaries or invade bone
- As the sarcoma grows, it compresses surrounding normal tissue to form a **pseudocapsule**, which contains a compression zone and a reactive zone
- The reactive zone comprises edema, inflammatory cells, and tumor cells
- Microscopic tumor cells perforate through and extend beyond the pseudocapsule

The single most frequent site of distant metastasis is lung (70%)

Bone, liver, and brain involvement is less common

Perez & Brady

Rarely spread to lymph nodes……

Lymph node involvement rates:

- Clear cell sarcoma (10% to 18%)
- Cutaneous Angiosarcoma (10% to 15%)
- Rhabdomyosarcoma (20% to 25%)
- Epithelioid sarcoma (20% to 35%)

Sarcomas in which Lymphatic Metastasis is seen - can be remembered by the mnemonic **RACE For MS**

R: **R**habdomyosarcoma
A: **A**ngiosarcoma
C: **C**lear cell sarcoma
E: **E**pithelial cell sarcoma

For: **F**ibrosarcoma

M: **M**alignant fibrous histiocytoma
S: **S**ynovial cell sarcoma

Clinical Features

Depends upon the site of involvement

- Usually present as a lump or a mass, Often painless
- Slow growing over weeks to months
- If in retroperitoneal location, GI bleed, incomplete obstruction or pressure symptoms may occur
- May be associated with an episode of injury or prior radiation exposure
- Most common in extremities (lower > upper) but can occur anywhere in body

'Listen to your patient; they are telling you the diagnosis'

HISTORY TAKING SEQUENCE

Presenting (principal) symptom (PS)

History of presenting illness (HPI)

Details of current illnesses
Details of previous similar episodes
Current treatment and drug history
Menstrual and reproductive history for women
Extent of functional disability

Past history (PH)

Past illnesses and surgical operations
Past treatments
Allergies
Blood transfusions

Social history (SH)

Occupation, education
Smoking, alcohol, analgesic use
Overseas travel, immunisation
Marital status, social support
Living conditions

Family history (FH)

Systems review (SR)

"I already diagnosed myself on the Internet. I'm only here for a second opinion."

Diagnostic Work Up

- Complete History & General physical examination
- Routine blood Investigations –
  - CBC, LFT, KFT, RBS, Serum electrolytes, Viral markers
- Imaging - Evaluation of the primary site as well as potential sites of metastasis
  - Chest X-ray, MRI, CT Scan, PET-CT

- **A simple Chest X-ray is sufficient for low grade or small superficial high grade extremity sarcomas**
- **CT scan Thorax is recommended to rule out pulmonary metastases especially in deep or large high grade extremity sarcomas but may give false positive results due to small, indeterminate pulmonary nodules**
- **CT scan abdomen is preferred for primary sarcomas in abdomen because air-tissue interface and motion artifacts often degrade MRI quality**
- **MRI: For STS of the extremity, trunk, or head and neck, MRI is preferred over CT scan.**
- **PET-CT is useful for determining early response to systemic therapy for STS and has role in identification of unsuspected sites of metastases in recurrent high grade tumors**

Biopsy

- Following appropriate imaging assessment the standard approach for confirmation of diagnosis, histological grade and histologic type is **multiple core needle biopsy**
- Incision or core-**track** should be placed in the lesions that can be completely excised at the time of definitive resection
- **Excisional biopsy** is more practical option for lesion <3 cm but it should be avoided for lesions > 3 cm.
- **FNAC** has disadvantage of limited sampling & lack of tissue architecture, not suitable for molecular diagnosis. Usually used for confirmation of recurrence.

IHC, Molecular testing, cytogenetic testing

Histological Grading

- Under histologic grading, the most important criteria appears to be **Differentiation**, **Mitotic index** and the **Extent of Tumour Necrosis**
- Evaluates degree of malignancy and predicts outcome, mainly chances of distant relapse
- The two systems most widely used grading system are **NCI** & **FNCLCC**

Histological grading according to FNCLCC	
Tumour differentiation	
Score 1	Closely resembling normal tissue
Score 2	Histological typing is certain
Score 3	Embryonal or undifferentiated sarcomas
Mitotic count (per 1.7 mm^2)	
Score 1	0-9 mitoses per 1.7 mm^2
Score 2	10-19 mitoses per 1.7 mm^2
Score 3	>19 mitoses per 1.7 mm^2
Tumour necrosis	
Score 0	No necrosis
Score 1	<50% tumour necrosis
Score 2	≥50% tumour necrosis
Histological grade	**Grade 1: total score 2, 3** **Grade 2: total score 4, 5** **Grade 3: total score 6, 7, 8**

FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer.

TNM Staging (AJCC 8th Edition)

The **major changes in the eighth edition** of the AJCC staging for soft tissue sarcomas are the following **four** points :-

- Tumors are described separately according to the 4 primary sites :
  - ❑Head and neck
  - ❑Extremities and Trunk
  - ❑Abdominal & thoracic Viscera
  - ❑Retroperitoneum

- **AnyT,N1,M0** tumor in the trunk and extremity is classified as stage IV, whereas for the retroperitoneal tumor, **anyTN1M0** remains as stage III B

- Tumors in the trunk, extremity and retroperitoneum, **tumor size** classified into four categories: (a) ≤5 cm; (b) >5 cm and ≤10 cm; (c) >10 cm and ≤15 cm and (d) >15 cm

- The notation about the depth of the tumor (superficial or deep from the superficial fascia) has been eliminated

Prognostic factors

- **Stage**: TNM stage of the tumor is the most powerful predictor for DFS and OS. Five-year DFS for stages I, II and III STS are 86%, 72% & 52% respectively.
- **Grade**: Important individual prognostic factor. High grade has poor survival rates.
- **Size**: Tumors ≤ 5 cm have better prognosis than > 5 cm
- **Site**: Tumors located in the head and neck or retroperitoneum have lower survival rates than those with tumors located in the extremity or superficial trunk
- **Depth**: Tumors close to body surface have better prognosis than deep growing tumors

Histologic subtype

- MPNSTs, leiomyosarcoma and epithelioid sarcoma have worse prognosis

Lymph node

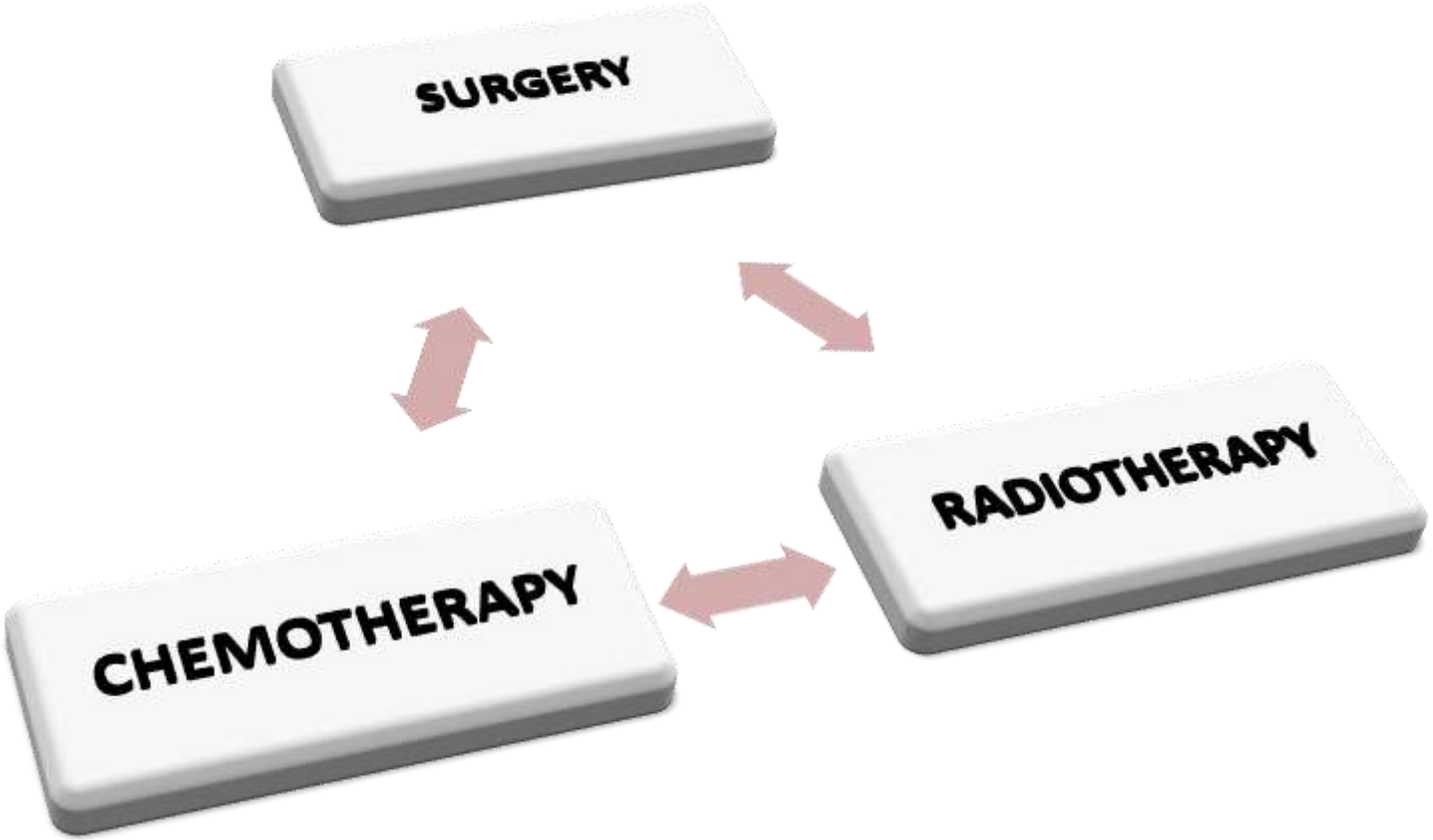
- LN involvement for STS is rare, but if present, it is an adverse prognostic factor

✓ Distant recurrence is associated with **tumor size**, **depth** & **grade, recurrent presentation.**

✓ Significant predictors for Local Recurrence include **positive margins** of resection, **recurrent disease** at presentation, **older age**, and **head and neck or retroperitoneal location**

✓ **Bone invasion** & **neurovascular invasion** are bad prognostic factors

Principles of Management of STS



Management

Multidisciplinary Team Approach

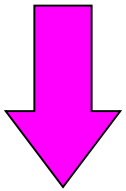
- Surgeons – Multiple Specialties
- Radiation Oncologist
- Radiologist
- Pathologist
- Occupational & Physiotherapist

Paradigm shift

- **Changing trends -**

Extremity sarcomas

Amputation



Limb Preservation

- NCI trial- Rosenberg et al – **Amputation = Limb salvage**
  (Comparable Survival)

- Limb salvage rates: **60% - 1970 = 90% -1990**

Surgical Management

Broad Principles

Appropriate surgical resection- a prerequisite for curative treatment of STS

Surgical options

Marginal resection/excisional biopsy ("shell out" procedure)	*LR 50-90%*
Wide en bloc resection/Conservative surgery/Limb sparing surgery (removes cuff of normal tissue)	*LR 25-60%*
Radical resection/Amputation (entire anatomic compartment including muscles & neurovascular structures)	*LR 00-18%*

Perez and Brady's Principles and Practice of Radiation Oncology (7th edition)

R - Classification

R0	The surgical margins are macroscopically and microscopically negative for tumor cells
R1	A surgical margin is microscopically contaminated with tumor cells or the tumor was marginally resected along its pseudocapsule
R2	An intralesional tumor resection was performed

Surgical Management

Wide resection/Conservative surgery:-

Surgical resection in the form of ***limb sparing surgery*** is main treatment for extremity STS.

- Prefer wide en bloc resection with **≥1 cm margin**.
- For histologic subtypes **DFSP and Myxofibrosarcoma** ≥2 cm margin.
- Some low grade subtypes: **< 1** cm may be taken
  - Eg. WD liposarcoma: even R1 resection is adequate.
- Skin to be removed if involved or shows neovascularization.
- Periosteum and/or perineurium can be removed to provide an adequate margin when soft tissue sarcoma abuts the bone or major nerves.

Surgical Management

Wide resection/Conservative surgery:-

- After unplanned surgical excision Re-excision should be considered if possible.
- Amputation to be reserved for rare cases only; no DFS benefit seen, though local control is better.
- Limb-sparing surgery with **a planned positive surgical margin** is sometimes accepted.

  *In a study by **Gerrand et al**. LR rates resulting from **procedures with planned positive margins** **to those of procedures with unplanned positive margins** a 4% LR found in former compared to 32-38% LR for the later.*

After Surgical Management:-

- Observation:
  - ≤5cm, low grade lesions with negative margins after surgery.
  - Pts with large > 5cm, low grade Atypical lipomatous tumors (ALTs) with negative margins.

But for most high grade sarcomas, wide resection alone is not enough and it is combined with pre or post-op RT.

What I would like from my Surgeon

- Place metallic clips at boundaries of resection
- Skin exit point of drain to be near the incision
- Bury the neurovascular bundle if exposed and mark the site with a clip
- Please give me clear radial margins; RT boost does not improve results, better to re-excise for clear margins

Radiotherapy

- Neoadjuvant (Pre op)
- Adjuvant (Post op)
- Intra-op
- Definitive RT

Techniques

- Conventional EBRT
- IMRT / IGRT / Particle beam
- Brachytherapy

Neo adjuvant (Pre op)

Indications:

- If tumour is adjacent to or involving the critical structures
- Likely difficult resection
- Tumour initially inoperable at diagnosis.

EBRT Doses

Pre-op: 45- 50.4Gy preop. @1.8- 2Gy/#/Day.
+/- 16-20 Gy EBRT boost post operatively
(if margins +ve)

Adjuvant (Post op)

Indications of adjuvant radiotherapy :

Low Grade	▪ **T Size > 5 cm** ▪ **Margin +ve** ▪ **Locally recurrent disease,** ▪ **Excision without prior staging** ▪ **Tumor location not amenable to salvage surgery**
High Grade	▪ **All**

Post-op: (3-6 wks post surgery) 60-66 Gy delivered in 1.8 or 2 Gy/# for –ve margins & 66-68Gy for +ve margins

For gross residual 70-76 Gy.

Perez and Brady's Principles and Practice of Radiation Oncology (7th edition)

Pre Op vs Post Op RT

	Pre op RT	Post op RT
Advantages	- Lower RT dose - Smaller Tx volume - Tx volume well defined - Improved resectability - Better oxygenation of tumor cells - Fewer long-term toxicities	- Entire pathology specimen and final margins are available.
Disadvantages	- Delays definitive management (surgery). - Risk of poor wound healing after Sx	- Target less clearly defined - Anatomic planes disrupted; larger margins needed for EBRT. - GI loops tethered within treatment fields, higher toxicity. (abdominal RT) - Long-term toxicities

Pre-op RT vs Post-op RT: which approach is superior, remains unclear.

Intra op/ Brachytherapy

Intraoperative radiotherapy (IORT) is a technique where

- A high, single fraction radiation dose is delivered during surgical procedure in operation theatre to macroscopic tumor bed.
- Leads to minimal exposure of surrounding tissues which can be displaced and shielded during the procedure

Methods :

- ***IOERT***
- ***IOHDR (flab method)***

Intra op/ Brachytherapy

Advantages	✓ **Radiation applied directly to tumour bed** ✓ **Minimizes radiation damage to surrounding tissue** ✓ **No delay in radiation to allow for tumour repopulation and hypoxia** ✓ **Shortens treatment time with possible cost reduction**
Disadvantages	✓ **Well equipped and shielded OT with appropriate radiation safety** ✓ **Dedicated equipment's (Mobile LINAC, HDR Brachytherapy machine)** ✓ **Needs local expertise in IORT or brachytherapy** ✓ **Requires close cooperation between surgeon and oncologist. Multi disciplinary team work.**

Brachytherapy

Brachytherapy as monotherapy can be used in

- Medium sized tumours (<10cms)
- High grade
- Negative surgical margins
- Preferable primary lesion
- Re-irradiation

Brachytherapy + EBRT

EBRT will add to benefit along with Brachytherapy in

- BT cannot adequately cover
  - unfavourable geometry/ OAR restriction
  - skin ulcer
- High risk of recurrences
  - >10cms

Brachytherapy

Advantages

- ✓ **As applicators are in tumor bed- high dose to target and rapid dose fall off- reduced dose to normal tissues**
- ✓ **This could translate to lower risk of lymphedema/ sub cut fibrosis/ bone fracture**
- ✓ **Short duration of treatment**
- ✓ **Early treatment in post op period has shown to improve LC (avoiding tumor repopulation, efficacy in less hypovascular/ fibrosed tumor)**

Disadvantages

- ✓ **Limited as compared to EBRT in its volume coverage**
- ✓ **Depends on skill of the radiation oncologist**

Brachytherapy

- LDR BRT as monotherapy
  - 45-50 Gy over 4-6 days
- LDR BRT in combination with EBRT
  - 15-25 Gy at 0.45 Gy/hour over 2-3 days
- Fractionated HDR
  - 3-9 Gy/Fraction once or twice daily
  - No consensus
  - Can be given as Out-patient
- IOHDR BRT
  - 10-15 Gy at 0.5 cm depth to supplement EBRT
  - No Data for specific role

When not to do Brachytherapy?

- Location very close to skin/ skin compromised
- Irregular tumour bed with doubtful catheter stability/ possibility of kink
- Acral and phalangeal sites.

Definitive RT

- In unresectable disease or patients with medical contraindications to surgery, high dose RT may be given with or without concurrent chemotherapy.

RT dose 70-76 Gy in 35 38 #

Particle beam therapy

Particle beam therapy has also been attempted in these cases with **protons**, neutrons and carbon ions.

- Particle beams such as protons and heavier ions (carbon ions) have more favorable physical and biologic characteristics than photons, which make them appealing for clinical use. Specifically, because of the ***Bragg peak*** dose distribution property, can be created with ***steep dose fall off*** at field borders. This allows for ideal sparing of adjacent critical normal structures as well as opportunities for safe dose escalation.

- There are several single-institution reports for protons that show very good results. Local control rates for ***skull-base chordomas*** treated with protons range from 46% to 90% and for skull-base chondrosarcomas range from 75%-100%.

Chemotherapy & Targeted agents

- **NACT**
- **ACT**
- **CRT**
- **Palliative in metastatic setting**

- ✓ **doxorubicin** and **ifosfamide** remains the most effective chemotherapy drugs available for the treatment of majority of these tumors.
- ✓ Other agents like **taxane** and **gemcitabine** in combination has shown benefit.
- ✓ Many targeted agents like Imatinib, Pazopanib, Trabectedin, Eribulin has been tested in different situations with mixed results.

Neo adjuvant Chemotherapy

Indications of NACT:-

- Chemoresponsive histology
- Disease is only potentially resectable
- Pts who require extensive resection eg. disarticulation, amputation, or hemipelvectomy.

May be used in the **neoadjuvant** setting if a **chemoresponsive histology** has been documented.

- Leiomyosarcoma – doxorubicin, gemcitabine, trabectedin
- Synovial sarcoma – Ifosfamide, doxorubicin
- Uterine stromal Sarcomas – Ifosfamide, doxorubicin
- Myxoid round cell liposarcoma -- trabectedin

Concurrent Chemo radiotherapy

- There is no consensus as to the optimal approach to CRT.

- Some centers use concomitant CRT with single agent Doxorubicin while others use sequential RT and an anthracycline + ifosfamide based chemo regimens.

- Most data available pertain to the use of chemotherapy in the adjuvant setting only.

Adjuvant Chemotherapy

Indications:

- high grade tumors with large tumor size > 10 CM,
- +ve margins,
- gross residual disease
- Recurrent disease
- Synovial sarcoma, Myxoid liposarcoma

- Anthracyclines are the agents most active against sarcomas.
  - Doxorubicin is the conventional first line agent, alone or in combination. Ifosfamide is also considered first line.

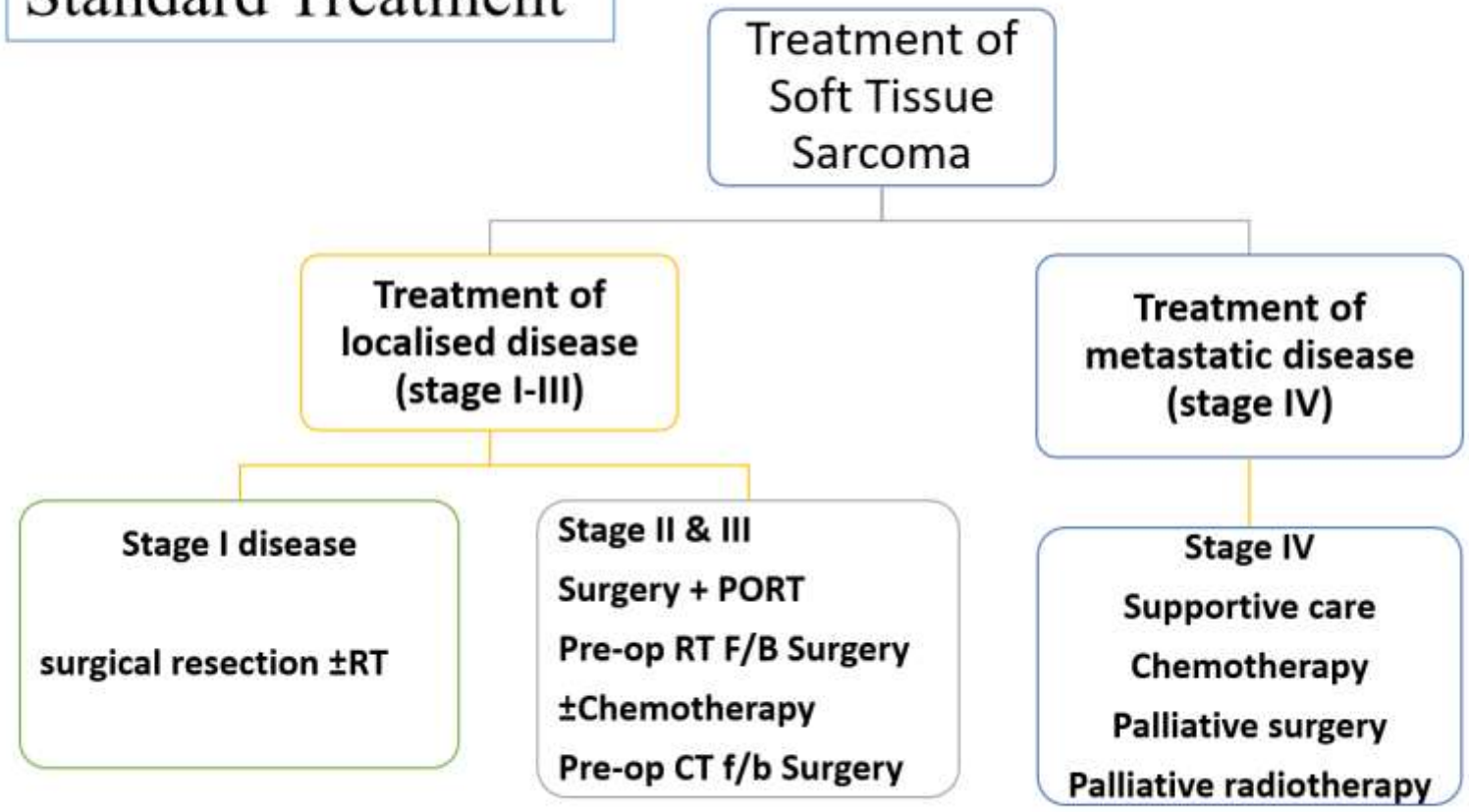
- Most trials in the adjuvant setting involves small numbers.
  - Probably because RT is more often preferred as adjuvant therapy.

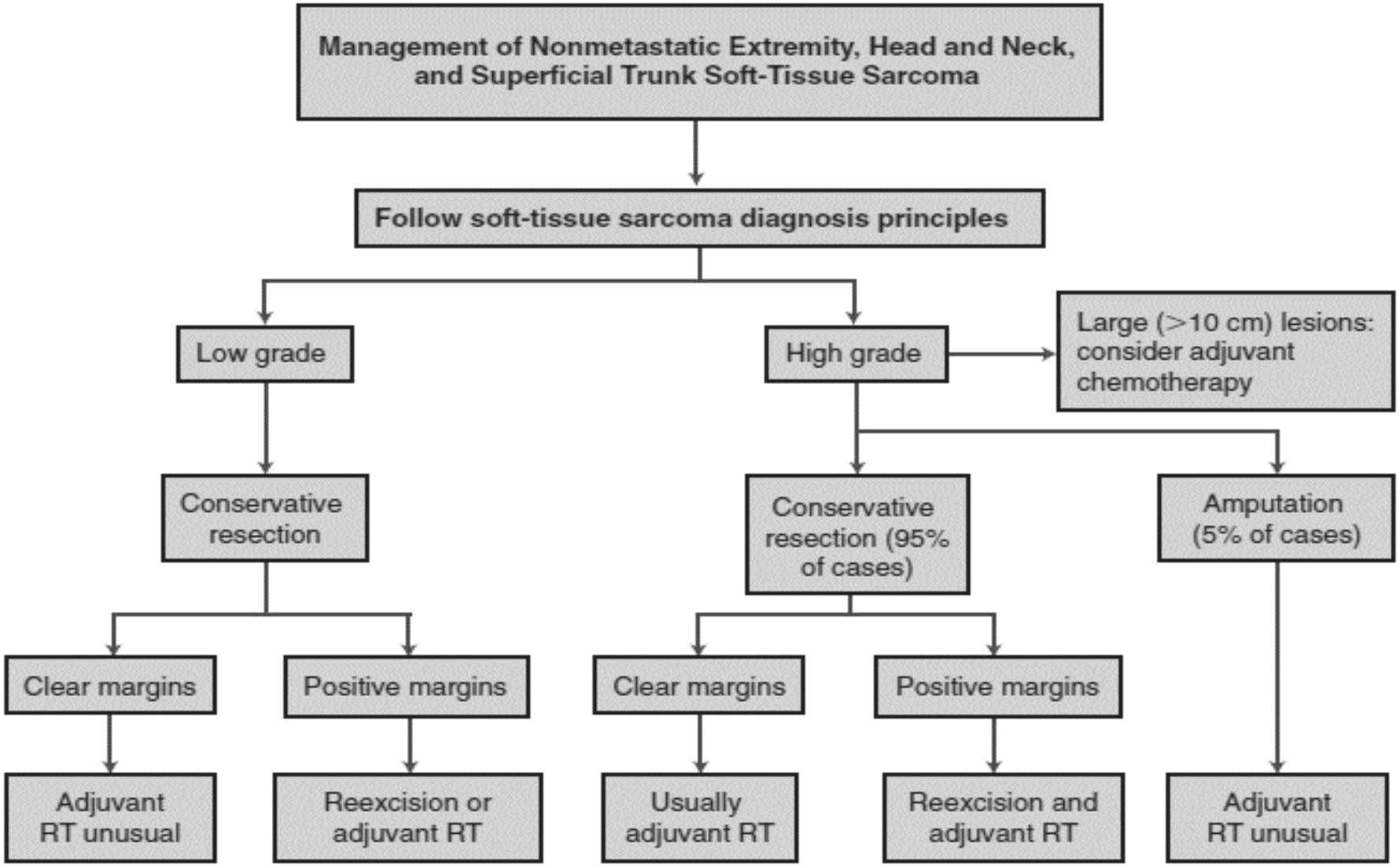
Chemotherapy for Metastases

Targeted therapies are a newer form of drug therapy than chemotherapy.

Targeted Agents		
Imatinib	TKI	GIST
Pazopanib	Multiple TKIs	Non adipocytic STS
Bevacizumab	VEGF-R	Vascular origin sarcoma (investigational)
Flavopiridol	CDK4	WD Liposarcomas
Trabectedin	Cell cycle blocker	Adipocytic sarcomas/myxoid round cell liposarcoma & LMS
Eribulin	Microtubule inhibitor	Liposarcoma, LMS

Standard Treatment




Management of Nonmetastatic Extremity, Head and Neck, and Superficial Trunk Soft-Tissue Sarcoma
Follow soft-tissue sarcoma diagnosis principles
Low grade
High grade
Large (>10 cm) lesions: consider adjuvant chemotherapy
Conservative resection
Conservative resection (95% of cases)
Amputation (5% of cases)
Clear margins
Positive margins
Clear margins
Positive margins
Adjuvant RT unusual
Reexcision or adjuvant RT
Usually adjuvant RT
Reexcision and adjuvant RT
Adjuvant RT unusual

Complications of treatment

Complications/ toxicities are due to SURGERY/ RADIOTHERAPY/ CHEMOTHERAPY

1. Wound complications
   - Poor wound healing appears as a problem mostly in extremity sarcomas.
2. Bone fracture
   - Factors that reduce this risk:
     - Lower dose to bone
     - Lower target volume.
3. Peripheral nerve damage
4. Fibrosis
5. Joint stiffness & edema

Follow up

Surgically-treated intermediate-/high-grade patients may be followed every 3–4 months in the first 2–3 years, then twice a year up to the fifth year, and once a year thereafter.

Low-grade sarcoma patients may be followed for local relapse every 4–6months, with chest X-rays or CT scan at longer intervals in the first 3–5 years, then annually.

Take home messages

- Multidisciplinary approach
- Multimodality treatment
- History and work up
- Exact staging, grading and IHC is mandatory
- Safe surgical margin (R0 resection)
- Organ/Limb function preservation
- Role of RT
- Prognostic significance of Chemotherapy

Thank you