Soft tissue Sarcoma: Overview

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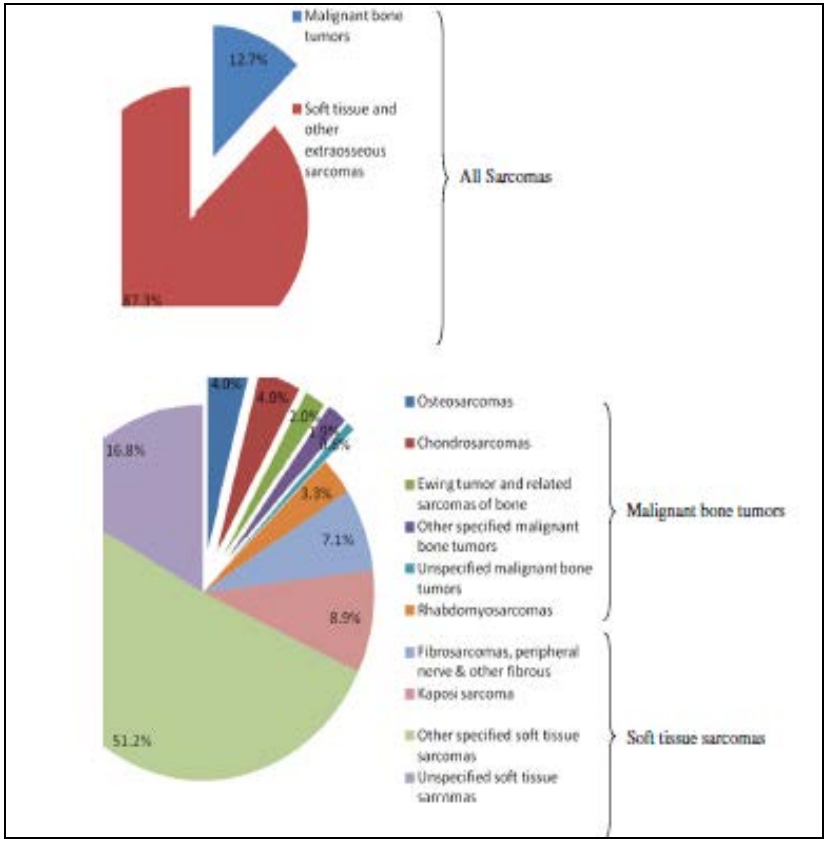
- Epidemiology
- Pathology
- Natural History
- Workup
- Treatment

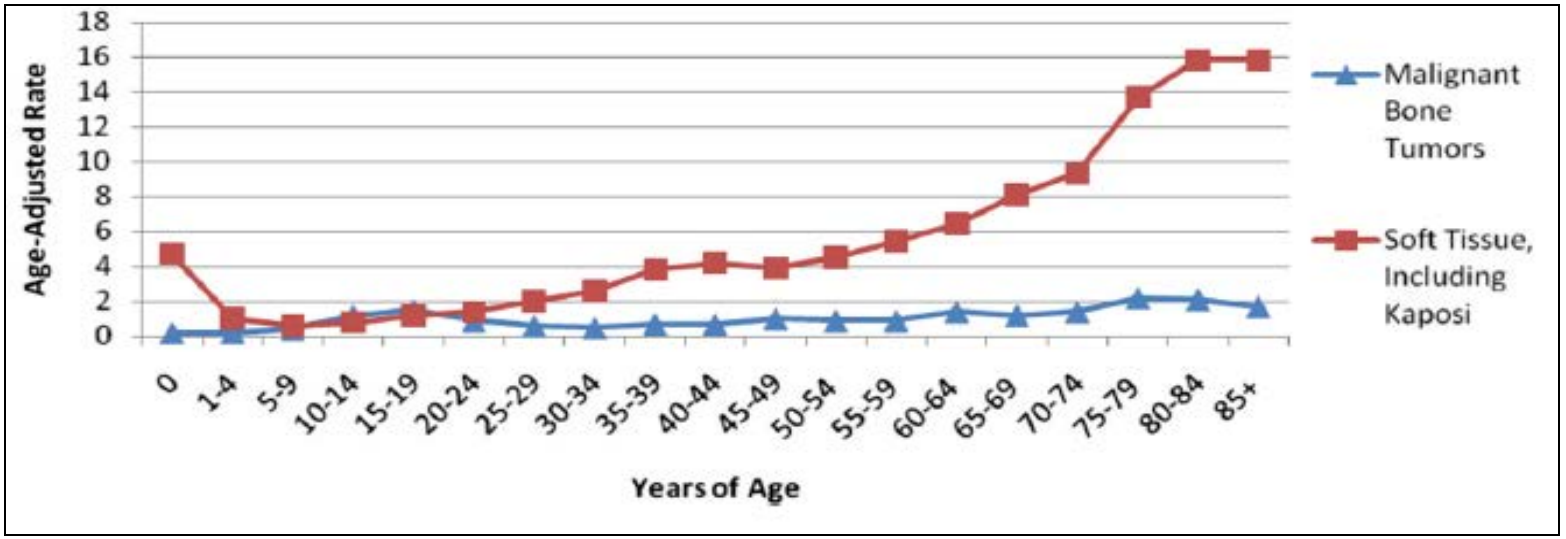
Epidemiology

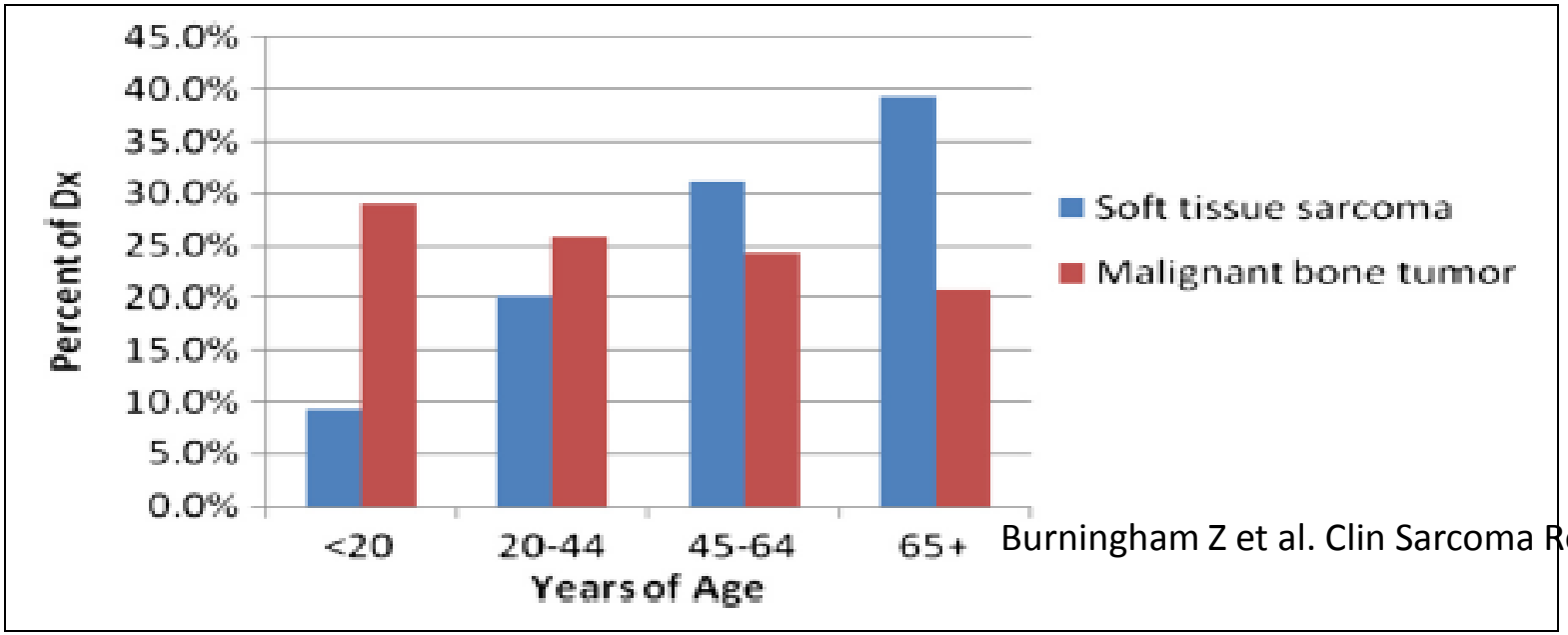
- Multiple malignancies at multiple sites
- 21% Pediatric solid tumor
- 1% adult solid tumor
- 87% of all sarcoma are STS
- Osteosarcoma & Chondrosarcoma : MC Bone
- “Other “ MC is Sarcoma



Burningham Z et al. Clin Sarcoma Res 2012

Epidemiology(SEER database 2004-08)





Burningham Z et al. Clin Sarcoma Res 2012

Epidemiology : India

- 0.9% of all cancer: Sarcoma
- EWS and Osteosrcoma : MC Bone sarcoma

Ramaswamy A et al. SAJC 2016

Aetiology

- Race and geography:
- Exact data lacking
- Comparable incidence rates through out the world.
- EWS more common in white
- STS more common in Black

Genetics

NF 1	10% EWS
TP53 (Li Fraumeni)	Paediatric RMS
TP53 (Somatic)	30-60% STS
RB mutation	Leiomyosarcoma
Hereditary RB Survivors	OGS (500 fold risk than gen pop)
FAP (Gardner's Syndrome) (5q21)	Desmoid Tumor
Carney's Startakis Syndrome (SDH B mutation)	GIST
RAPADILINO Syndrome	OGS
Rothmund Thomson Syndrome II	OGS
Werner Syndrome	OGS
Bloom Syndrome	OGS
Diamond Blackfan Anemia	OGS

- Reproductive and Obstetrics factor:
- Non-significant association with:
- Age of 1st childbirth (>29yrs) (OR 3.16)
- Toxemia during Pregnancy (RR 2.71)
- High Birth weight (>4.065gm) (OR 1.35)
- Congenital Hernia (with EWS) (RR 6.67)

Burningham A et al.. Clin sarcoma Research 2012

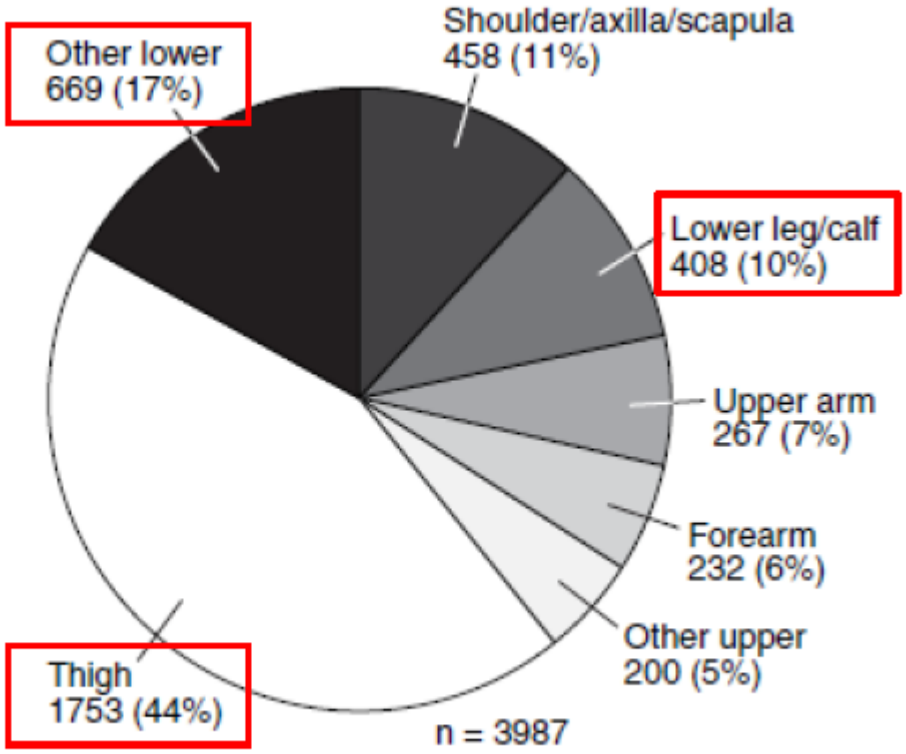
- Infection (adult Sarcoma)
- HHV 8 (Most Common): Kaposi’s Sarcoma
- Both in HIV + and HIV -
- HIV: Kaposi’s Sarcoma
-

- Radiation (SIR :4.2)
- Less in low dose Ionizing Radiation (RR 7.5 per Gy)
- STS MC secondary cancer after RT
- RT in Breast, Lymphoma, GU, HNC
- 16 fold increase of Angiosarcoma after Breast RT
- Average time period 10yrs
- Histotype:
- Pleomorphic MFH (26%)> Angiosarcoma (21%) Fibrosarcoma (12%)>LMS (10%)>MPNST(9%)

- Lymphedema:
- Lymphangiosarcoma
- Specially after PMRT (in & outside RT field)
- Filariasis

- Occupation exposure and lifestyle
- Bone tumor:
- Wood, cork and straw factory (OR 3.57)
- Radiology worker (SIR 2.88)
- Chlorophenol exposure (OR 1.79)
- No significant relation with Tobacco or alcohol
- Trauma anecdotal in Desmoid tumor

Distribution



Brennan M, et al. Ann Surg 2014;260:417.

Pathology

- Heterogenous group of mesenchymal malignancies
- HP + IHC
- May have distinct genetic correlation
- May have distinct clinical course with distinct outcome

- **WHO subtyping (Soft Tissue Tumor):**
- Benign
- Intermediate (locally aggressive)
- Intermediate (Rarely metastasizing)
- Malignant

Pathology

- Most common types:
- Undifferentiated/unclassified sarcoma (pleomorphic/round cell/spindle cell) (Pleomorphic MFH)
- Liposarcoma
- Leiomyosarcoma
- Synovial sarcoma
- Malignant peripheral nerve sheath tumor (MPNST)
- Rhabdomyosarcoma
- Primitive neuroectodermal tumor (PNET) /extraskeletal Ewings
- Angiosarcoma
- Ephitheliodsracoma
- Clear cell sarcoma
- Alveolar soft part sarcoma
- Solitary fibrous tumors

Myxofibrosarcoma(formerly MFH)

- Common : Malignant
- Infiltrates centimeters beyond the visible/palpable mass and when deep can invade usual barriers
- Higher rate of positive margins
- Commonly in the extremities
- Greater risk of local recurrence (up to 30%)
- 5yr OS 60-70%

Dermato fibrosarcoma Protuberans(DFSP)

- Benign (rarely metastasizing)
- + CD34
- Rare but common cutaneous form
- WLE (2cm margin) TOC [5yr LR <5%]
- R1/R2 LR>50% needing Adj RT
- Rarely mets to lung (after high grade transformation)
- Imatinib in advanced and metastatic diseases

Lipoarsarcoma

- Common 50-60yr (20% adult STS)
- Any site
- Common:
- Thigh (24% of all extremity STS)
- RP (45% of all RP STS)
- Subtypes (distinct Clinico-pathology):

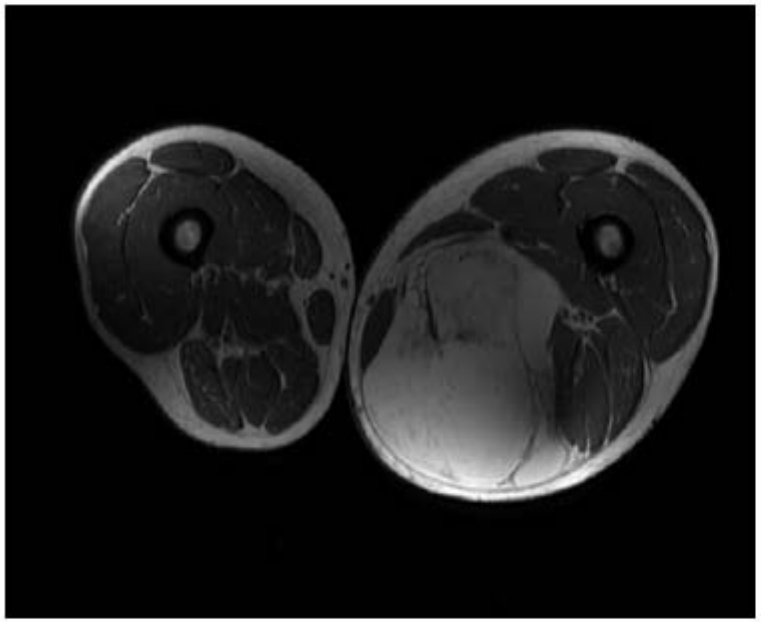
1. Well-differentiated(WD)/dedifferentiated LPS/Atypical Lipomatoues Tumor (ALT)
2. Myxoid/round cell LPS
3. Pleomorphic LPS
4. Mixed

WDLS/ALT

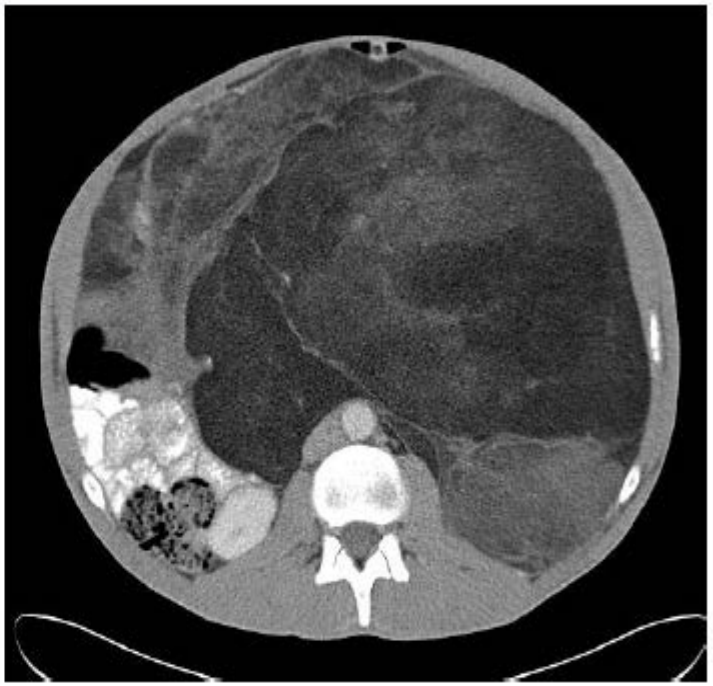
- CDK4/MDM2/HMCA2 amplification
- Has a ‘pushing’ growth pattern
- Occurs Extremity muscles (most common)
- Retroperitoneal (RP)
- Variety of other sites
- Behavior is different in limb vs. RP
- Recur less frequent and late
- Not develop metastases
- Dedifferentiation is uncommon (0-6%)
- Managed by marginal excision alone
- 5yr DFS 83%

SommervilleSMM, et al. ANZ J Surg. 2005;75:803. Weiss SW Am J SurgPath .1992;16:1051.

Atypical lipomatous tumor



Well-differentiated liposarcoma



Myxoid/Round cell LPS

- Mean age in mid 40's
- Extremity MC (66% deep thigh)
- Unusual metastatic Site: Soft tissue,RP (not Lung)
- Pure Myxoid : Low grade (5yr DFS 90%)
- >5% Round cell : High Grade (5yr DFS 50%)
- Exceptionally high S to Radiotherapy and Ifosfamide/Trabectedin

Myxoid LPS -dramatic responses to radiation

- McGill 50 patients, evaluated response to RT
- median decrease in tumor volume:
- <1% for high grade sarcomas
- 13.8% non-myxoid low grade sarcomas
- 82.1% myxoid liposarcomas

RobergeD, et al. RadiotherOncol.2010; 97:404.

Pleomorphic LPS

- High grade aggressive rare LPS
- Median age >50yrs
- Resembles undifferentiated/unclassified variety
- Upper extremity < Lower extremity
- Lung metastasis >50% cases
- Responsive to Ifosfamide/Gemcite

Leiomyosarcoma

- Vascular Smooth muscle origin (SMA/Vimentin +ve)
- Middle age
- Any site: RP>Pelvis>uterine body
- Vascular outflow obstruction common
- Surgery Primary treatment
- RP lesion are large/high grade
- Recurrence risk >50%

Malignant peripheral nerve sheath tumors(MPNST)

- Originate from peripheral nerves
- 50% occur in patients with NF type I
- S-100 +ve̅ (High Grade less S100+)
- Most common in the extremities, trunk, H&N
- NF1 associated worse outcome than sporadic
- WLE +/- RT : TOC
- NACT (RR 20%) : Ifosfamide/Doxorubicin
- Sorafenib : Investigational

Angiosarocma (including lymphangiosarcoma)

- Uncommon
- Commonly associated with Lympoedema (Stewart Treves Syndrome) and RT (Breast Ca Commonly)
- Arise in skin/subcutaneous tissue –most typically of the breast or H&N
- One of most common sarcomas seen after RT
- Chemo-responsive sarcoma-taxanes and anthra
- LR recurrences common (Median Survival 3yr)

Synovial sarcomas

- Young adult 15-35Yrs
- Originally thought to arise from the synovium of joints but actual origin is unknown
- t(X;18)(p11.2;q11.2)
- 2 types: monophaisc and biphasic
- 80% extremity (LE>UE)
- Histology that is more responsive to chemotherapy

Alveolar soft part Sarcoma

- Rare ,F>M,20years
- t(17-X)(p11.2;q25) [ASPSCR1-TFE3 fusion protein]
- LE>UE
- Initially slow growing, Low local rec after Sx
- Poor prognosis after metastasis
- Investigational: MET-I (crizo),Antiangiogenic (Sunitinib/Avastin)

Epitheloid Sarcoma

- Distal type (Hand & feet) and Proximal type (thigh, buttock) (Distal UE MC)
- Young adult
- Deep fascial spread (wide margin)
- >20% LN metastasis (LND if N+)
- Poor Prognosis (5yr OS 63%)
- Moderately S to CT/RT (Proximal more resistant and aggressive)

Desmoid tumor(Fibromatosis)

- 10-25Years, rare,
- Locally aggressive, non-metastatasing
- Mutation in CTBNN-1 gene that code beta-catenin
- Common site abdominal wall>extremity
- Incidence increased after Pregnancy
- Local Recurrence (variable) : 15% in 5yr
- Surgery : TOC

Indian Data

Author	STS subset	Remarks
Rekhi *et al.*[42]	Malignant triton tumors	Average age - 30 years 80% high-grade Mainstay of treatment - surgery Radiotherapy is effective
Rekhi *et al.*[43]	Epithelioid sarcomas (conventional and proximal type)	Common in extremities IHC markers - vimentin, EMA, CK, CD34, desmin Major treatment - surgery OS greater in conventional than proximal type Unfavorable parameters - deeper location, large size, high tumor stage
Jambhekar *et al.*[45]	Chordomas	Evaluation of brachyury expression in chordomas - 90.2% sensitivity
Rekhi *et al.*[46]	MPNST	Common in age >30 years More common in men 88.8% high-grade S-100-70.3% positivity 71.4% underwent surgery DFS - 53.1% Age <30 years, T size >5 cm, high-grade, high stage - prognostic
Rekhi *et al.*[48]	Alveolar soft part sarcoma	Median age 24 years Most common in the extremities TFE3 positive - 91%, desmin positive - 16%, SMA positive - 11% Multimodality treatment

STS=Soft tissue sarcomas, MPNST=Malignant peripheral nerve sheath tumors, IHC=Immunohistochemistry, CK=Cytokeratin, EMA=Epithelial membrane antigen, SMA=Smooth muscle actin, OS=Overall survival, DFS=Disease-free survival

Ramaswamy A et al. 2016

Clinical Presentation

Extremity

- Enlarging painless mass
- Pain
- Functional limitations
- Symptoms associated with compression of local structures

Clinical Presentation

Retroperitoneal

- Abdominal mass –often incidentally found
- Pain
- Gastrointestinal: early satiety, obstruction, bleeding
- Lymphedema, neurologic or musculoskeletal sx

Clinical Presentation

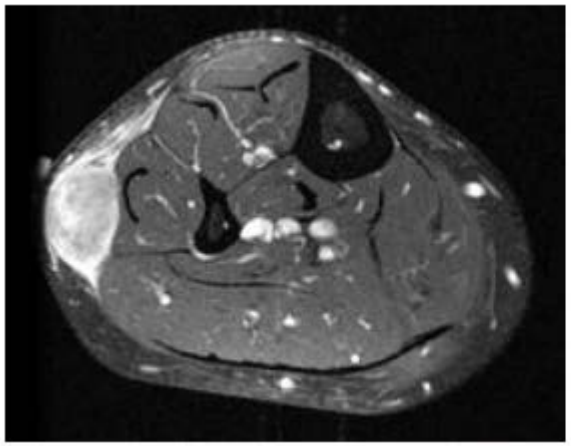
Rare

- Fevers/leukocytosis
- Paraneoplastic hypoglycemia (leiomyosarcoma)
- Symptoms from distant metastases

Patterns of spread

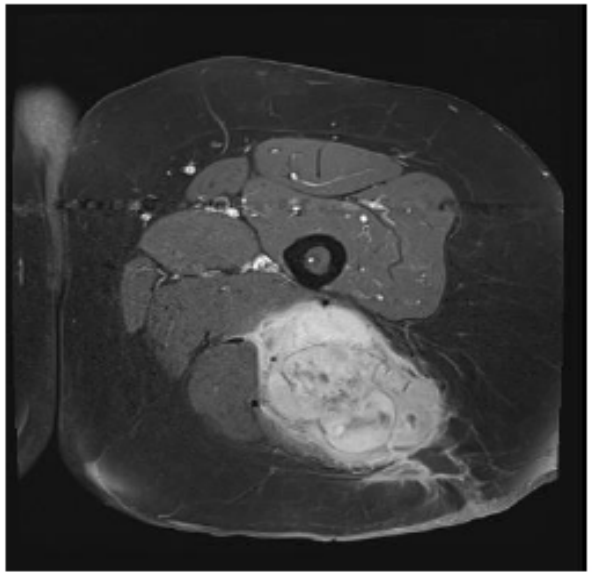
Extremity

- Along longitudinal tissue planes –within the compartment
- If involves nerves/vessels, can track along
- Compresses/distorts adjacent soft tissue
- Tumor can be well beyond the mass



← Subcut pleomorphic Sarcoma

→ Deep MPNST



Patterns of spread

Extremity

Hematogenous….predominantly to the lung*

At diagnosis 10%

Exceptions: myxoid liposarcoma

Lymphatic…..rare, except certain pathologies#

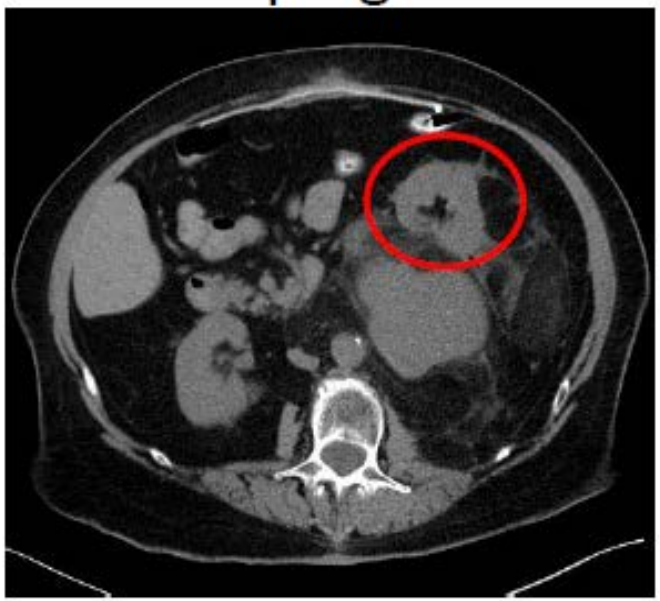
- Epithelioid(18%)
- Rhabdomyosarcoma (12%)
- Clear cell sarcoma (11%)
- Angiosarcoma(13%)
- Other reports: synovial cell, extraskeletal Ewings

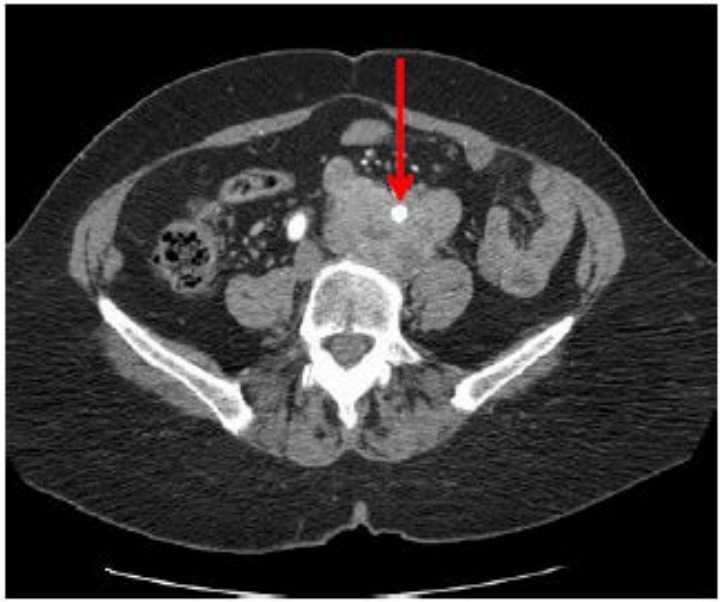
*Christie-Large M et al. EurJ Ca 2008; 44:1841.

#RiadS et al. ClinOrthRelRes 2004;426:129. Fong Y et al. Ann Surg1993; 217:72.

Patterns of spread

- Retroperitoneal
  - Pushing/displacing adjacent organs
  - Enveloping structures





Evaluation

- MRI : IOC
- Standard X ray to :

  rule out bone tumor

  bone erosion & risk of # if any

  calcification if any
- CT scan in RP tumors (yield is equal to MR)

Imaging

- MRI (+/- Dynamic contrast enhancement) may help in assessing prognosis & response to ChT.
- DCE MRI may act as surrogate for VEGF.
- Whole body MRI – alternative to PETCT in children for whole body staging.
- FDG PET in the initial staging can lead to tt optimisation particularly in EWS due to the superiority of FDG PET in detecting bone lesions.
- FDG PET- potential non-invasive surrogate for ChT response.

Guideline of Bone and STS, Puri A,Laskar S ,2011

Role and Indication of PET CT

- Appropriateness criteria for PET CT in bone and STS: (IAEA Human Health series 2009)

Indication for PET/CT in bone and soft tissue sarcomas	Relevance of Test
Staging	Potentially appropriate
Response evaluation	Potentially appropriate
Suspected recurrence	Potentially appropriate
Histological grading	Possibly appropriate

Role of FNAC

Tumor	Situation	Role of FNAC
Malignant Round Tumor Small Cell	Primary diagnosis	No; Can be used only if adequate material is obtained for immunohistochemistry and molecular analysis.
	Recurrence (early)	Yes.
	Recurrence (late)	No, biopsy is recommended as a second primary is a possibility.
	Metastasis	Yes.
Bone lesions	Primary bone lesion	No, (except in cases with typical clinical and classical radiological findings eg. Giant cell tumour of bone.)
	Suspected myeloma metastasis to bone	Yes.
Soft tissue tumours	Primary diagnosis	No; Sometimes cytological features may be confusing and exact grading and tumour typing may be an issue.
	Recurrence	Yes (but it might not distinguish florid reactive changes from low grade tumours).
Suspected inflammation / infection in Bone and Soft Tissue lesions		Yes, to rule out tumour.

Biopsy

- Principles
- Multiple core bx (14-16G) {Preferred}
- Excisional Bx in T<3cm (superficial)
- Incisional Bx in difficult cases (Longitudinal small incision)
- planned in such a way that the biopsy pathway and the scar can be safely removed by definitive surgery (except for RPS)
- The biopsy entrance point can be tattooed.
- The tumor sample should be fixed in 4% buffered formalin in due time.

IHC

EWS/PNET	MIC2/CDD99 FLi 1
OGS	Nil
Cartilage Tumor	?S-100/? SOX2
Synovial Sarcoma	CK,BCL2,Mic2 TFE 3 (New)
RMS	MyoD,Desmin,Myoglobin
LMS	SMA,Calponin Desmin,Myoglobin
Alveolar Soft Part Sarcoma	TLE 3 (New)
Chordoma	Brachyury (New)

Staging

American Joint Committee On Cancer (AJCC) Staging System

For intra

(7th ed, 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence for primary tumor
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm but not more than 10 cm
T4	Tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (N)

N0	No regional lymph node metastasis*
N1	Regional lymph node metastasis

*If regional node status is unknown, use N0, not NX.

Distant Metastasis (M)

M0	**No distant metastasis**
M1	**Distant metastasis**

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Low grade; mitotic rate ≤5/50 HPF
G2	High grade; mitotic rate >5/50 HPF

Anatomic Stage/Prognostic Groups

*Gastric GIST**

Group	T	N	M	Mitotic rate
Stage IA	T1 or T2	N0	M0	Low
Stage IB	T3	N0	M0	Low

Anatomic Stage/Prognostic Groups *(Continued)*

Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Small Intestinal GIST***

Group	T	N	M	Mitotic rate
Stage IA	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Note: Also to be used for omentum.

**Note: Also to be used for esophagus, colorectal, mesentery, and peritoneum.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Grading

Table 1. Federation Nationale des Centres de Lutte Contre le Cancer histological grading criteria

Tumour differentiation	Necrosis (macro and micro)	Mitotic count (n/10 high-power fields)
1: Well	0: Absent	1: $n < 10$
2: Moderate	1: <50%	2: 10–19
3: Poor	2: ≥50%	3: $n \geq 20$

The sum of the scores of the three criteria determines the grade of malignancy. Grade 1: 2 and 3; Grade 2: 4 and 5; Grade 3: 6, 7 and 8. Reprinted from [4] with permission of John Wiley & Sons, Inc.

NCI grading:

1. Histology
2. Location
3. Tumor Necrosis

Some tumor types not typically graded

- MPNST
- Epithelioid
- Clear cell sarcoma
- Angiosarcoma
- Extraskeletal myxoid chondrosarcoma
- Synovial sarcoma
- all felt to be high grade

management

- **Surgical principles:**
- R0 (>1cm) margin is the goal
- If possibility of R1/R2 (neurovascular proximity:

  Call Radiation Oncologist

  Put surgical clips
- Remove biopsy scar (tattooed)
- May need removal of adventia or perinureum (NV abutted)
- Dissection thru the uncontaminated normal tissue planes.
- Drain (suction /closed) site should be near to incision site(Scope of ReEx in future Rec

Basic Principle

- **All patients to be considered for organ conservation.**
- **All patients to be evaluated preoperatively for feasibility of Intraoperative Brachytherapy.**
- **R2 Sx should be considered for revision excision**

Unplanned excision: common phenomena

- Typically smaller
- Typically subcutaneous (mistaken for lipomas)
- Often low grade
- Residual disease24-74%

Re excision to be done
Inappropriate skin incision
PORT use higher
Similar local control with primary radical surgery
Higher rate of aggressive surgery: poor functional outcome

AlamandaVK, et al. J SurgOncol2012;205:662-667.
Fiore M, et al. Ann SurgOncol2006;13(1):110-117

Surgical Principle

- If R1/R2 in final pathology:
- Re Resection is the ideal
- Re Sx significant predictor for Local Control

Local Control	5 yr s	10 yrs	15 yrs
With Re Sx	85	85	82
No Re Sx	78	73	73

Zagars GK et al 2003

Lymphadenectomy

- **Long term survival benefit in cN+**
- Stage II-III: cN+

  Radical LND vs No LND

  Median survival 16.3m vs 4.3m

LND dissection cN+ stage II III STS

Fong Y Ann Surg 1993

Radiation Therapy

- **Situations:**
  Pre operative
  Intra operative
  Post Operative

- **Technique:**
  Conventional EBRT
  IMRT
  IORT
  HDR BT(ISBT)

PORT: evidences

- **Indications: (any)**
- R1/R2
- Deep seated tumor
- High Grade
- T>5cm

Limb salvage Sx + PORT: similar LC/OS with amputation

Sx + PORT vs Sx alone: PORT increases LC not OS

Rosenburg SA et al Ann Surg 1982
Yang JC et al. J Clin Oncol 1998
Pisters PW et al J Clin Oncol 1996

PORT : R0 situation

- **High grade:**
  >T1 (>2cm): PORT must
  T1 : no RCT: Radical ISBT > No adjuvant RT

- **Low Grade:**
  PORT may be avoided in (all must be present)
  superficial
  <5cm
  R0

Yang JC et al. J Clin Oncol 1998

PORT : ISBT vs EBRT

- No RCTs on Radical BT or EBRT
- Similar LC rates BT with/out EBRT
- Lesser Soft tissue complications and lesser hospital stay
- Radical BT can be done in appropriate patients if Intestinal needles can encompass whole tumor bed

Laskar S et al. Annals of Surg Onc 2007

Pre op RT vs PORT

- **Pre op RT issues:**
- Decreases Tumor spillage during surgery
- Thickened acellular psuedo-capsule helps R0 resection.
- Wound healing delayed
- Need -6 weeks gap (RT-Sx)

- **Evidences: RCTs**
- LC is higher in PreopRT
- OS marginally superior in PreopRT
- Significant long term Post op complications (>120days) in PreopRT
- PORT helpful in unknown margin
- PreopRT helpful in gross primary disease

Sullivan B et al Lancet 2002
Pollock A et al 2004

Surgery RT interval

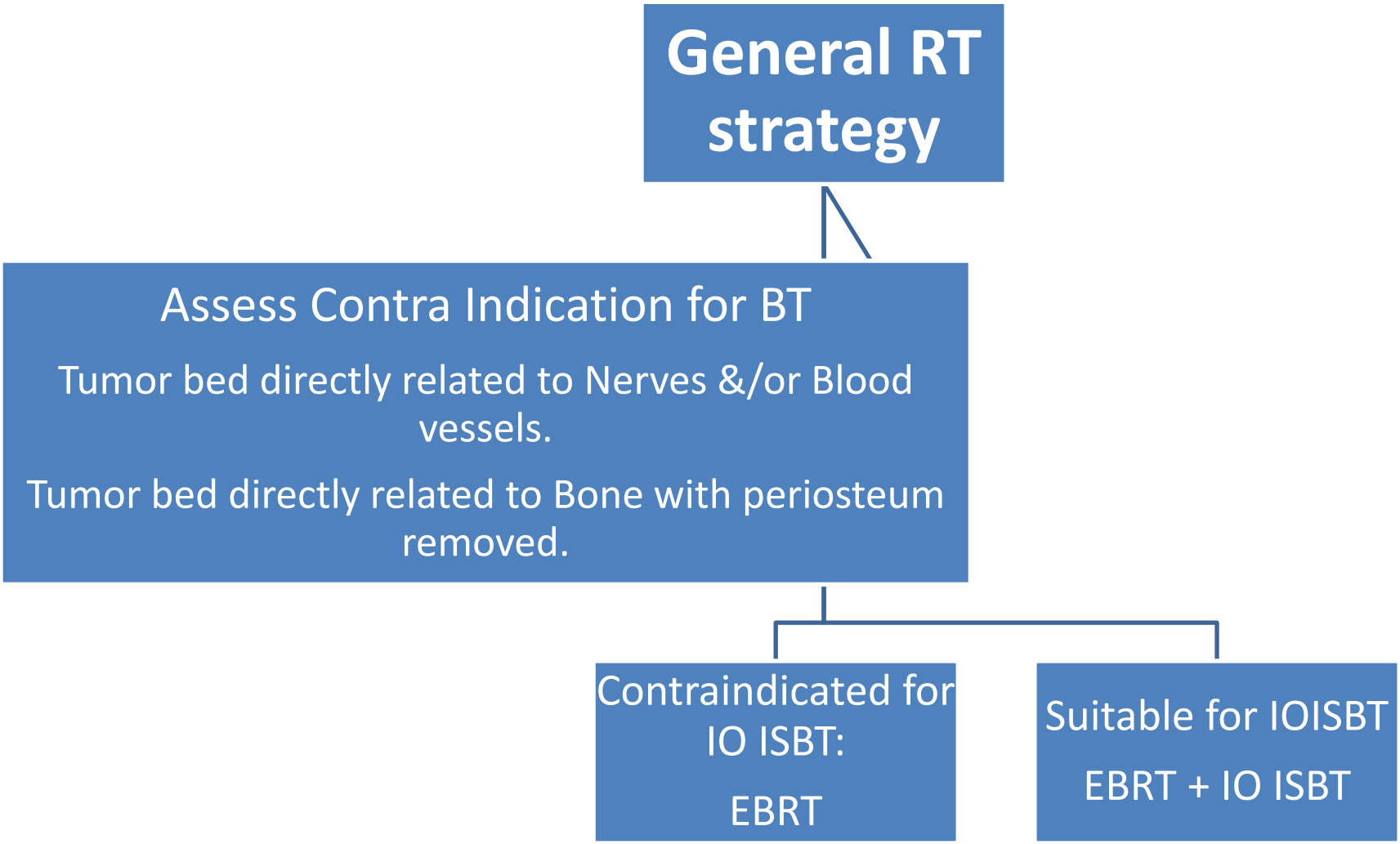
- Only one evidence:
- A delay between surgery and the start of RT of >30 days was associated with a decreased 10-year LC rate (76% vs. 83%, p = 0.07).
- May be due to an imbalance in the distribution of other prognostic factors
- **SX RT interval is not a potential prognostic factor for LC**

Ballo MT et al. IJROBP 2004

Role of IMRT in STS

- **Dose escalation feasible**
- **Specially helpful in Retro-peritoneal Sarcoma**
- **Local control improved**
- **Better normal tissue avoidance**

Alektier KM et al. J Clin Oncol 2008
Koshy M et al. Sarcoma 2003


General RT strategy
Assess Contra Indication for BT
Tumor bed directly related to Nerves &/or Blood vessels.
Tumor bed directly related to Bone with periosteum removed.
Contraindicated for IO ISBT:
EBRT
Suitable for IOISBT
EBRT + IO ISBT

Not suitable for IO-ISBT

- **EBRT:**
- Essential to spare at least 1.5 - 2.0cm of limb circumference from radiotherapy portal.
- Spare half circumference of uninvolved bone if possible.
- Try to keep uninvolved compartment out of radiation port as far as possible.

- **Dose:** Phase I - 50Gy / 25# / 5 weeks

  Phase II - R 0: 10 - 12Gy / 5 - 6# / 1 week

  R 1: 12 - 16Gy / 6 - 8# / 1 week

  R 2: 16 - 20Gy / 8 - 10# / 2 weeks

Suitable for IO ISBT

- Silver clips placed after excision of tumor to delineate the tumor bed.
- Brachytherapy catheters inserted uniformly to cover the entire tumor bed with 1.5 - 2.0 cm margin.
- Simulation and dosimetry to be done on 4-5th postoperative day.
- Dose prescription for brachytherapy - 0.5cm on either side of the implant plane.

- Brachytherapy Dose: LDR - 25 - 30Gy @ 45 - 50cGy / hr
- HDR - 21Gy / 7# @ 3Gy / # (2# / day with 6hrs gap)

- **Ext. Radiotherapy:**
- Radiotherapy to be started 3 weeks after completion of Brachytherapy
- Planning Target Volume: Gross tumor volume + 6 - 8cm margin

- Dose: After LDR Brachytherapy - 46 - 50Gy / 23 - 25# / 5 weeks
  After HDR Brachytherapy - 46 - 50Gy / 23 - 25# / 5 weeks

EBRT: Technicalities: extremity

Simulation: Customized immobilization

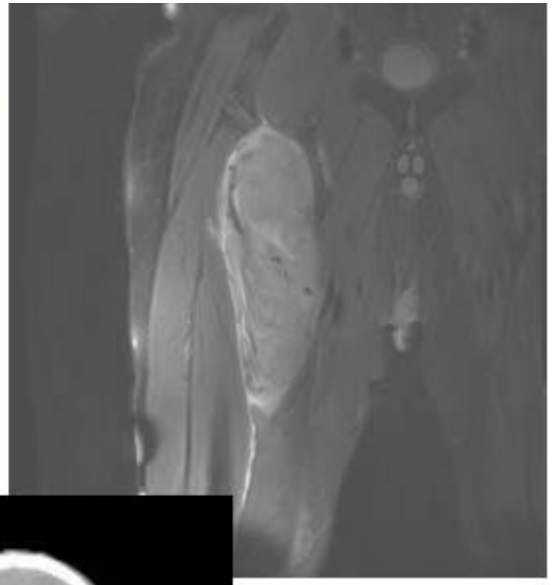
-Proximal extremity

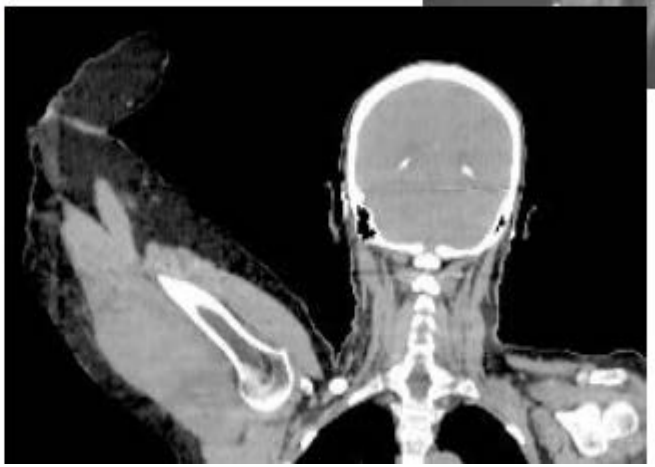
ST motion

skin folds

genitalia

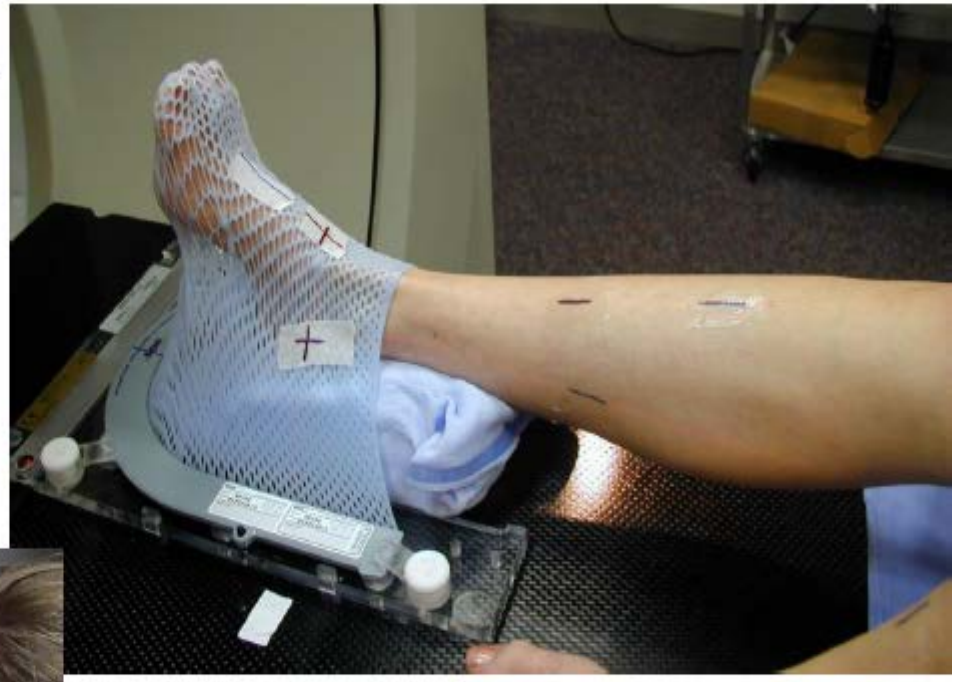
distance of arm to head





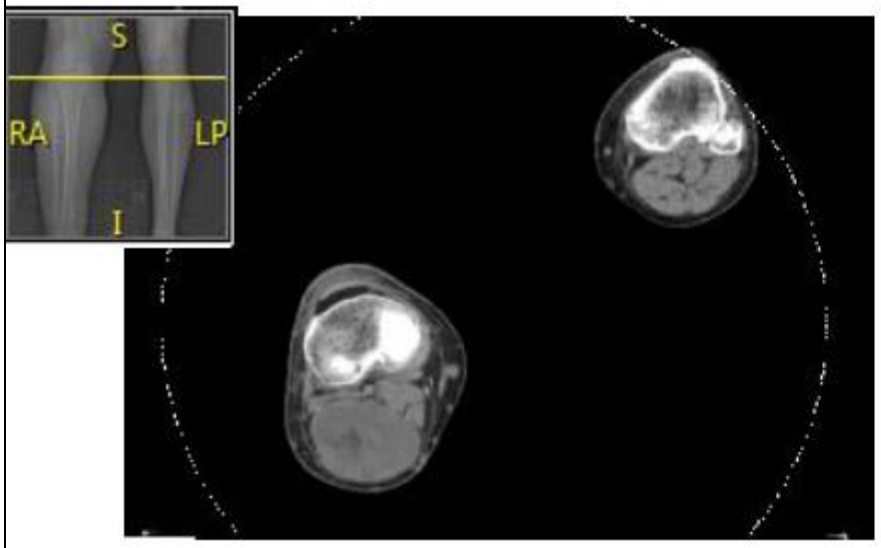
EBRT: Technicalities: extremity

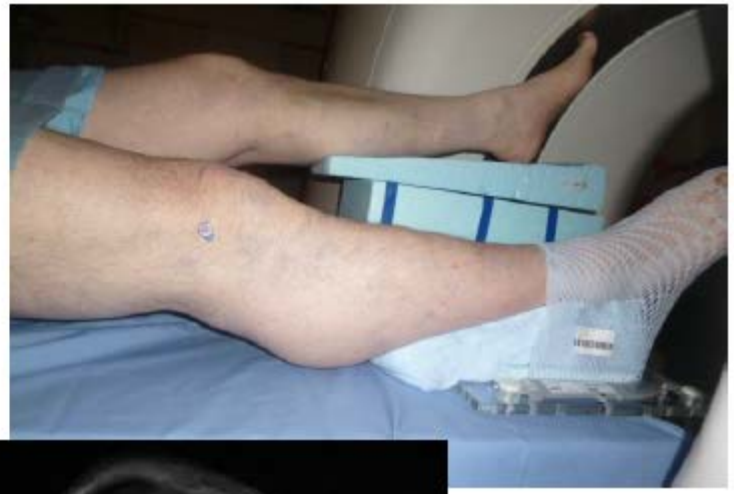
- Distal extremity -fixation to prevent rotation and move other limb out

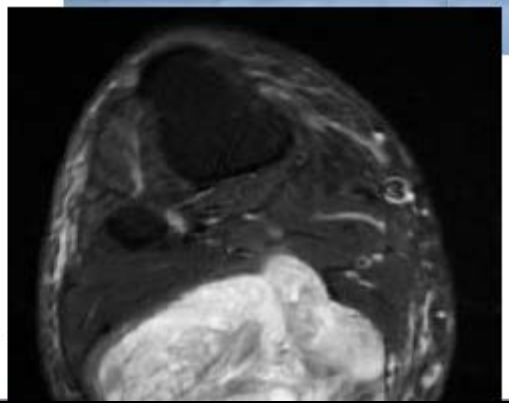


EBRT: Technicalities: extremity

- Mid extremity – let tissue be dependent if possible







Post op RT Target

CTV: shrinking field technique

Initial volume

- Surgical bed reconstructed from pre-op imaging
- Fusion of pre-op MRI with postop planning CT
- Further evaluation based on postoperative changes, operative and pathology report, surgical clips
- Expand volume 1.5 cm radially/4 cm longitudinally(TMH: grade II/III 6-8cm)

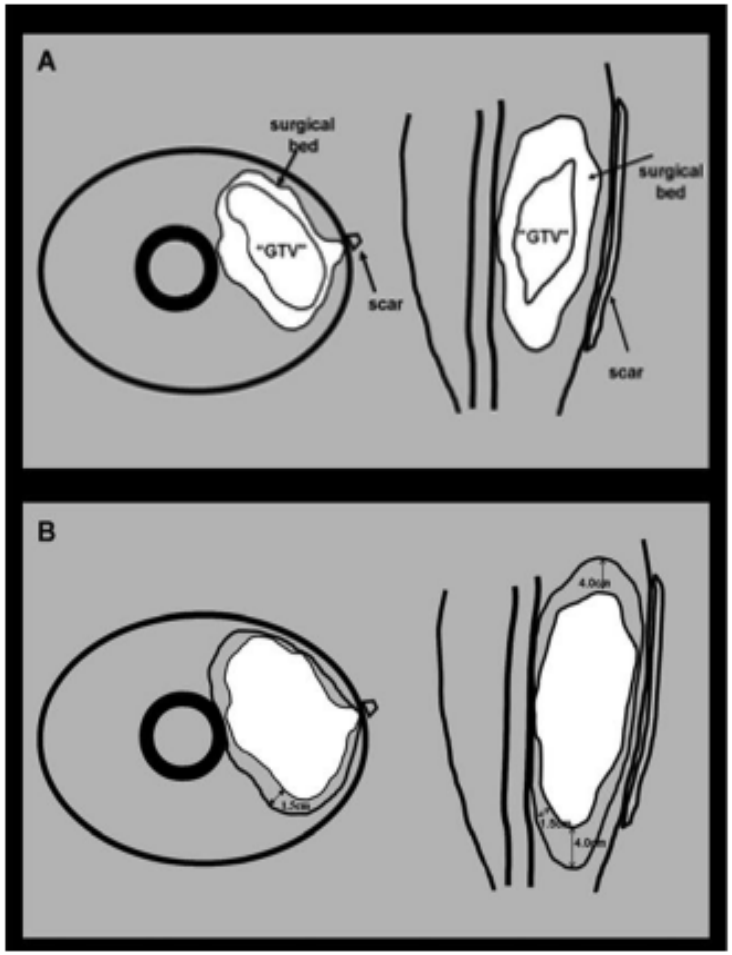
Haas RLM, et al. IntJ RadiatOncolBiolPhys. 2012.; 84(3):572-580.

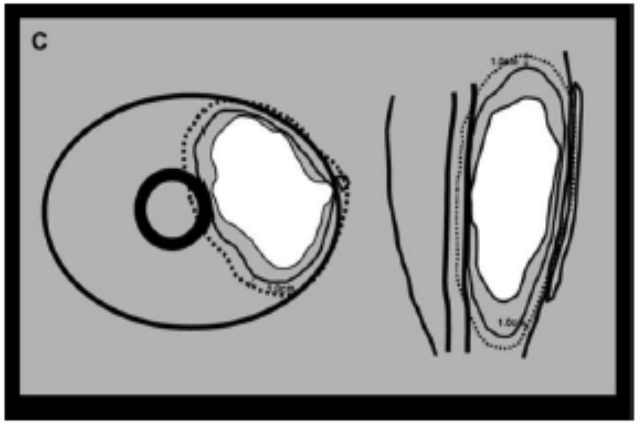
Post op RT Target

- **Boost volume**
- Same as initial volume except in the longitudinal
- Use GTV reconstructed with 2 cm (TMH:3cm) margins
- Other issue: scar/drain site to be included
- Low risk situations, drain site could be omitted

Haas RLM, et al. IntJ Radiat OncolBiolPhys. 2012.; 84(3):572-580.

Post op RT Target





ASTRO refresher course 2015

RT field and Local control

LR patients had significantly

- higher grade
- margin +ve
- recurrent disease
- more postoperative boost patients
- slightly older

60 LR patients vs 708 patients with no recurrence
LR patients: 82% (49/60) in-field
15% (9/60) out-of-field
3% (2/60) marginal

DickieCI, et al. IntJ RadiatOncolBiolPhys2012;82(4):1528-34.

Pre op RT

GTV:

- tumor seen on gad-enhanced T1 MRI
- Ideally done in treatment position
- Fused with planning CT images

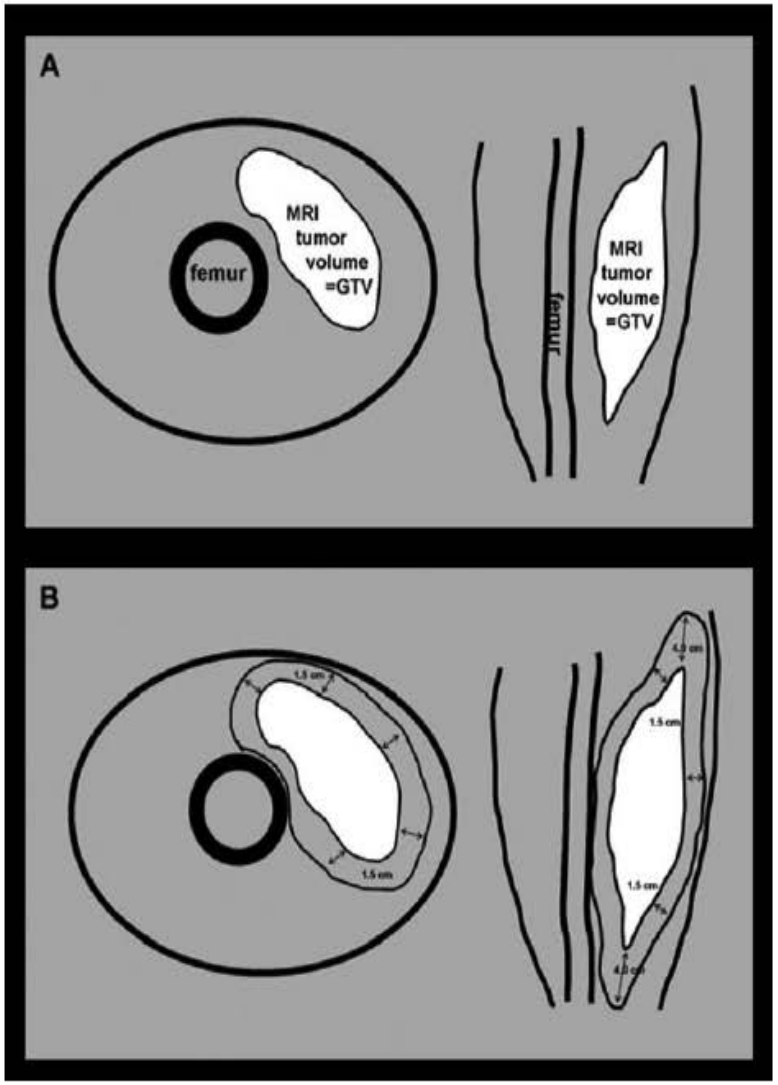
CTV:

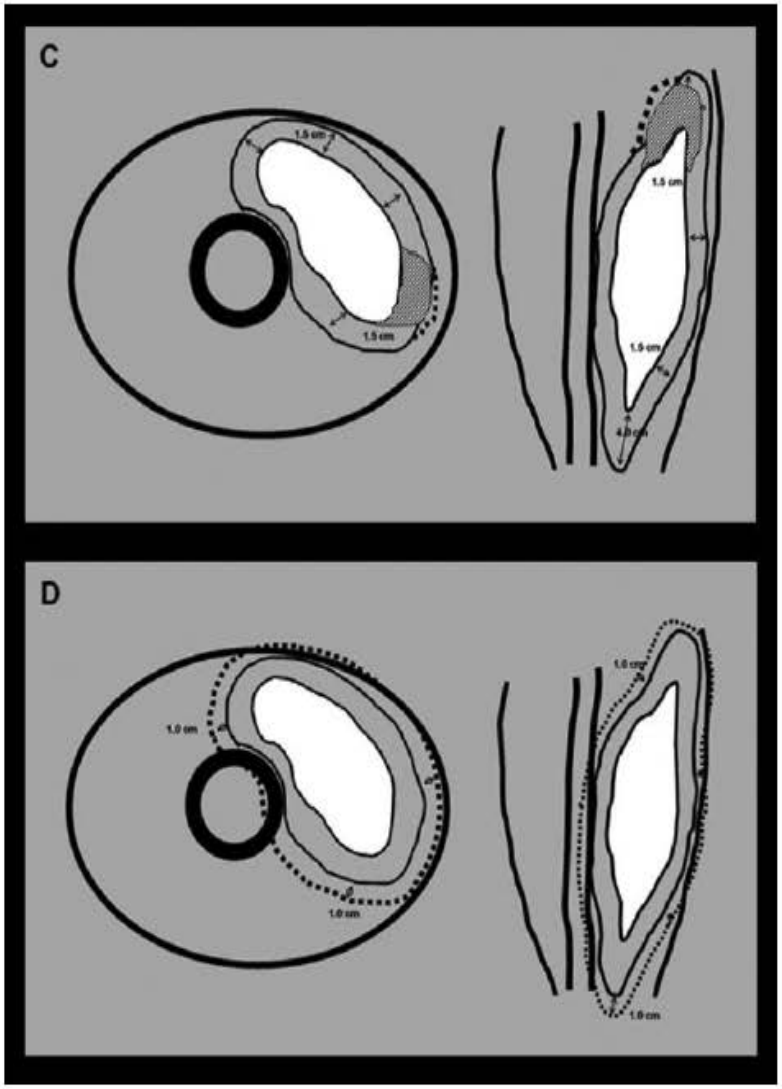
GTV +

- Longitudinally 3-4 cm (but limit it across joints/out of compartment)
- Radially 1.5 cm but limited at fascia/bone boundaries (unless involved)
- CTV should include peritumoral edema

Wang D, et al. IntJ RadiatOncolBiolPhys. 2011;81(4):e525-528

Pre op Target





ASTRO refresher course 2015

STS extremity : IMRT

Advantage

- Decrease dose to ‘normal structures’ : bone, soft tissue
- More conformity

Disadvantage

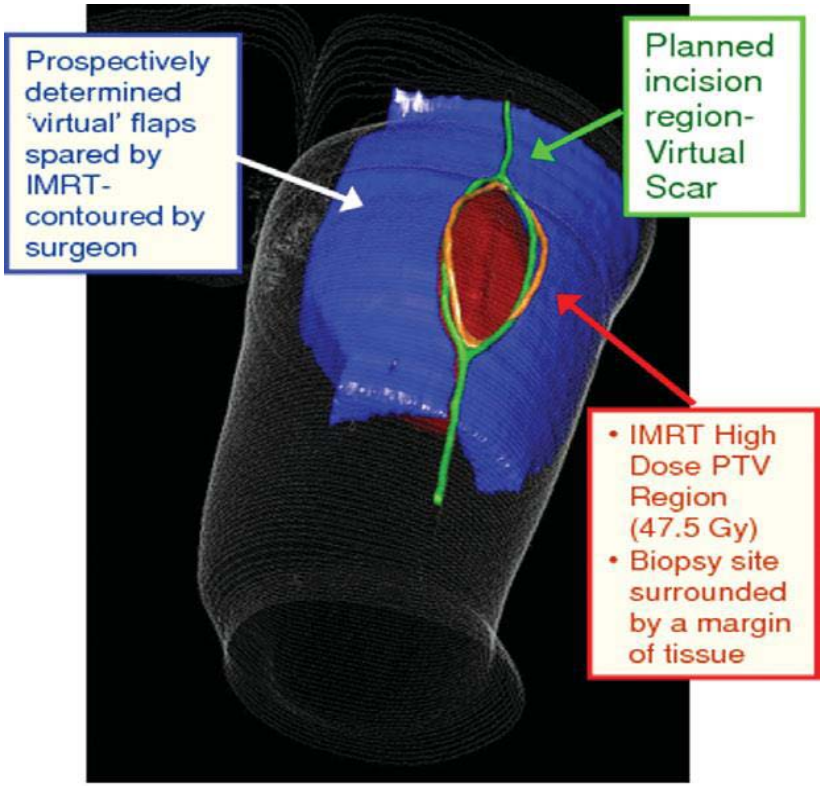
- Cost
- Higher dose to full circumference of limb
- Potential dose to other parts of the body (other limb/head)

Site : upper thigh

STS extremity : IMRT

- Use of IMRT with IGRT – decrease high wound complication rate
- Minimized dose to 'skin flaps' as determined in conjunction with the surgeon

- PTV: 50 Gy/25
- Flaps: <20 Gy



Multi-disciplinary STS phase II study protocol investigating high precision pre-operative IMRT to spare tissues from surgery and RT morbidity

ASTRO refresher course 2015

Head neck sarcoma

- **All patients to be treated with 3 D conformal radiation therapy**
- Planning Target Volume (PTV) shall vary according to exact site of disease.
- Dose: 66 - 70Gy / 33 - 35# / 6 - 7 weeks

DFSP

- **Extremities & Trunk: Post operative radiation to be considered if:**
  surgical margins +ve
  surgical margins close
  recurrent tumor

- **Mediastinum: Post operative radiation to be considered if:**
  surgical margins +ve
  surgical margins close
  surgical margins unknown
  recurrent tumor

Planning Target Volume (PTV): Gross tumor volume + 3cm margin.

Dose: 60 - 66Gy / 30 - 33# / 6 - 7weeks

High dose Tamoxifen & Chemotherapy – Investigational

STS: Retroperitoneum

Radiation issues

- Volume
- Patient GI stability
- Ability to spare normal tissues (meet constraints)
- Know kidney plans and function
- Preoperative vs. postoperative

STS: Retro-peritoneum

Postoperative RT

- Rarely can achieve adequate dose
- More gastrointestinal toxic

Preoperative RT

- Advantages
- tumor readily identifiable
- tumor displaces bowel
- potential tumor reduction
- Pseudo-capsule formation/margin improvement
- typically a lower dose is felt to be needed

STS: Retroperitoneum

- **Simulation:**
- Upper and lower body immobilization
- Oral contrast: for upper abdominal tumors
- IV contrast –to see psoas muscle invasion
- 4D simulation for upper abdominal tumors
- if organ motion > 1 cm consider gaiting

STS: Retro-peritoneum

GTV

- Register with MRI for muscle extent
- Create ITV to account for tumor motion

CTV

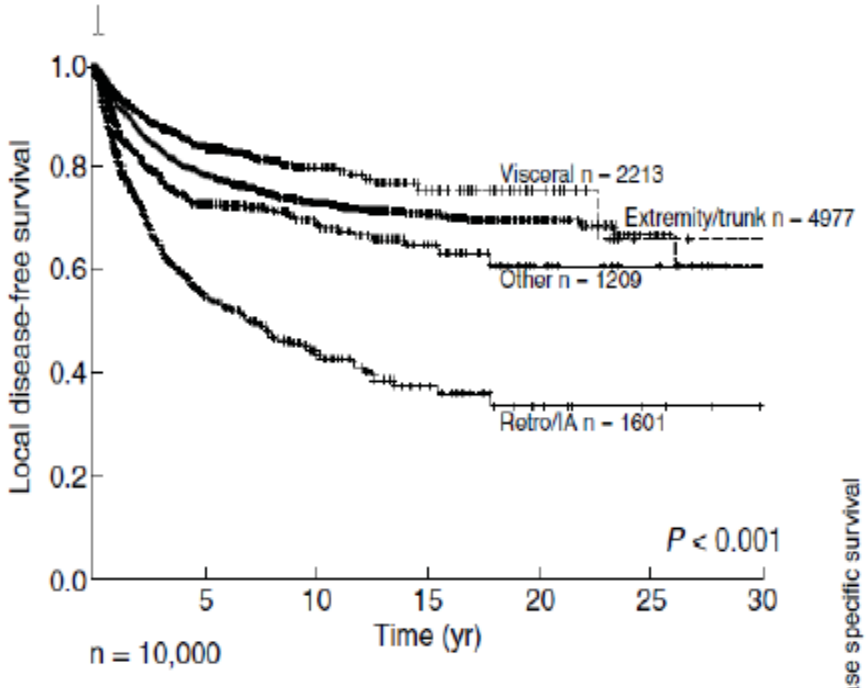
- GTV with 2-2.5 cm margin cephalo-caudal
- GTV with 1.5-2 cm margin radially
- Exclude: bone, kidney, liver
- Include rim of adjacent bowel/air cavity (5 mm)
- Include any disease extending to the inguinal canal

Baldini E et al IJROBP 2015

STS: Retro-peritoneum

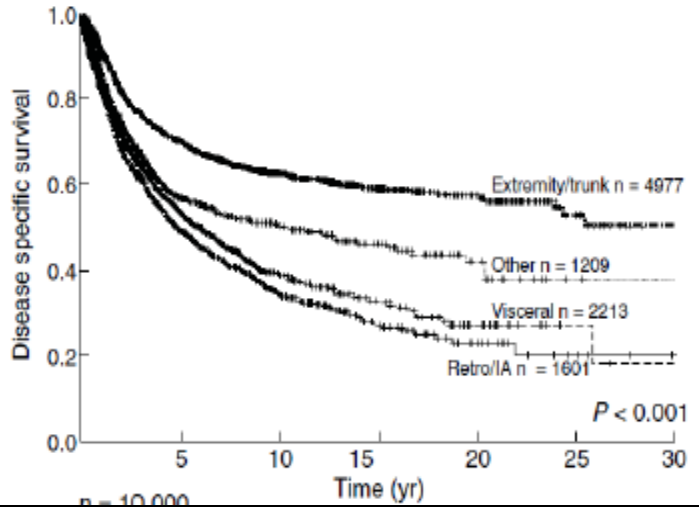
- **Dose escalation areas of high risk**
- IOERT
- IO ISBT
- CCB/SIB IMRT

STS: Retro-peritoneum

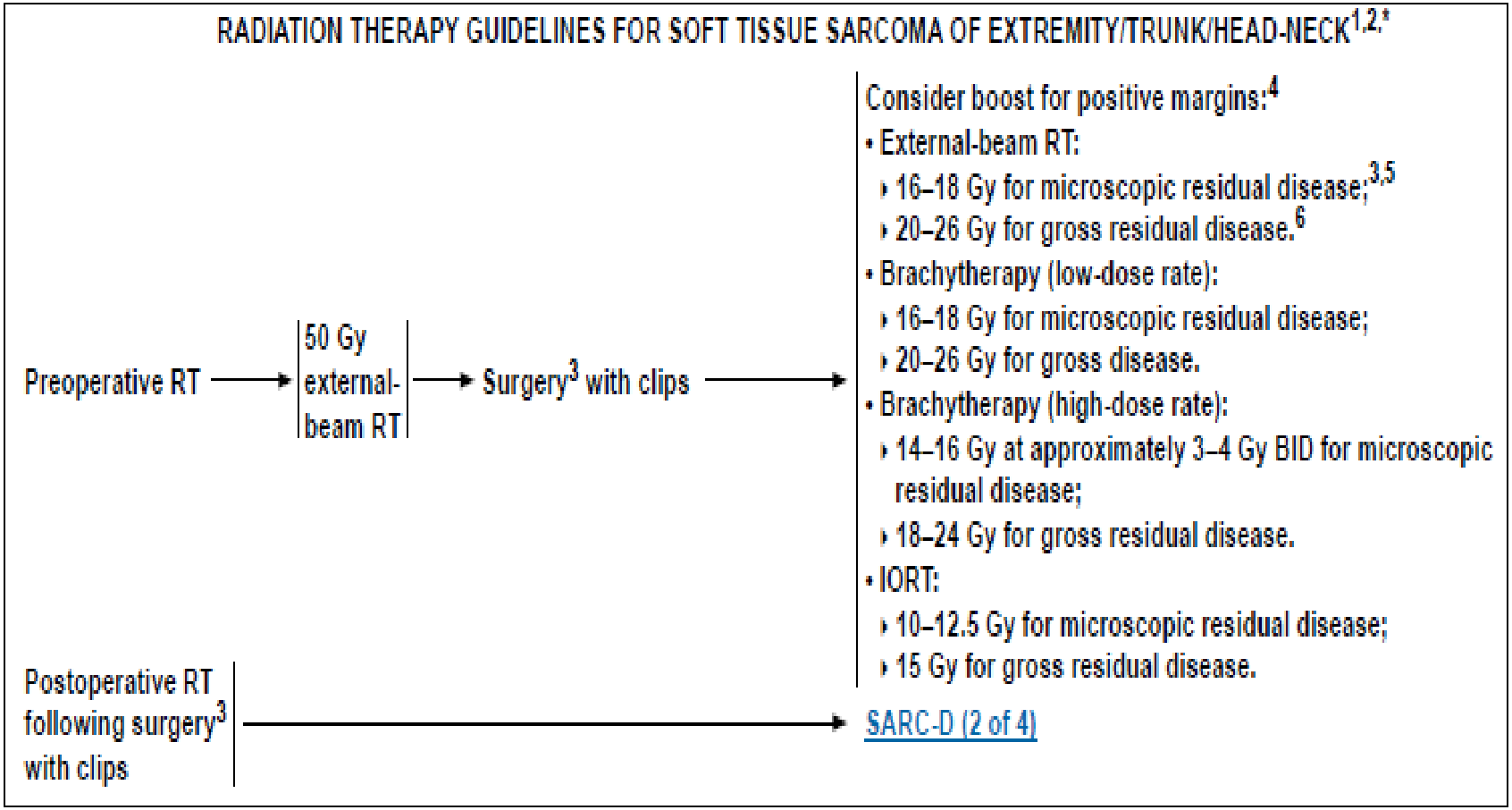


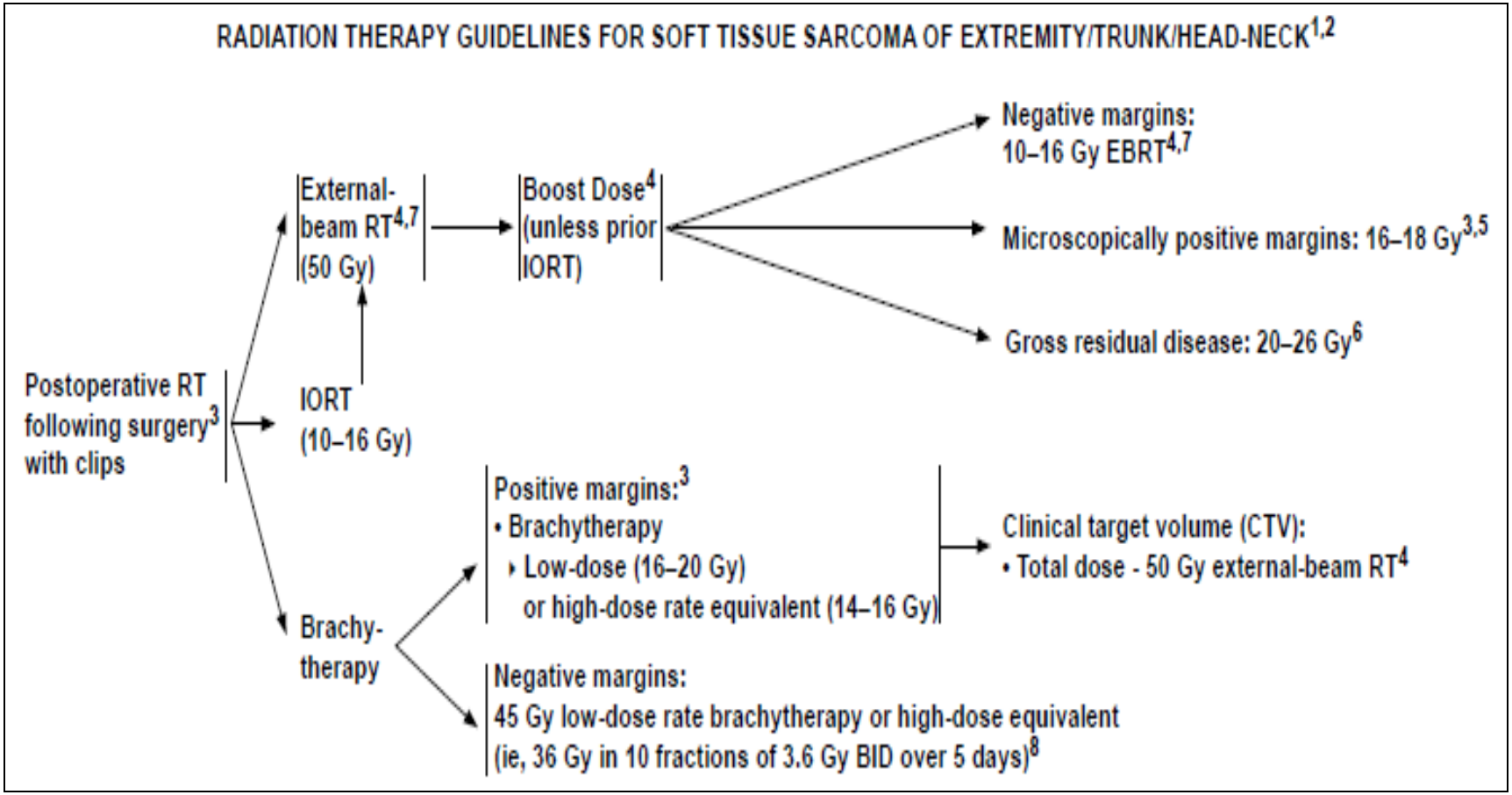
Outcome – significantly worse than other sites

- Local disease free survival
- Disease specific survival

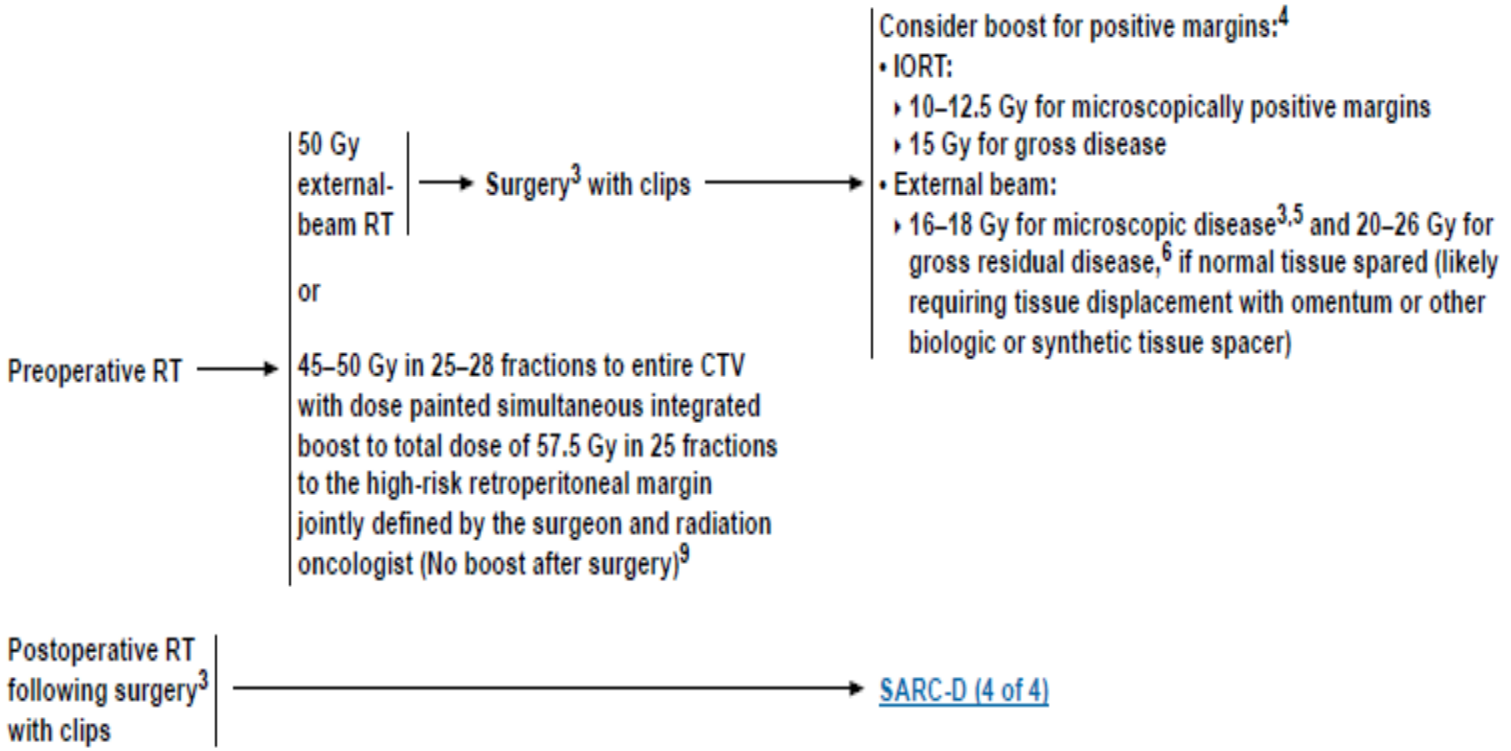


Radiotherapy

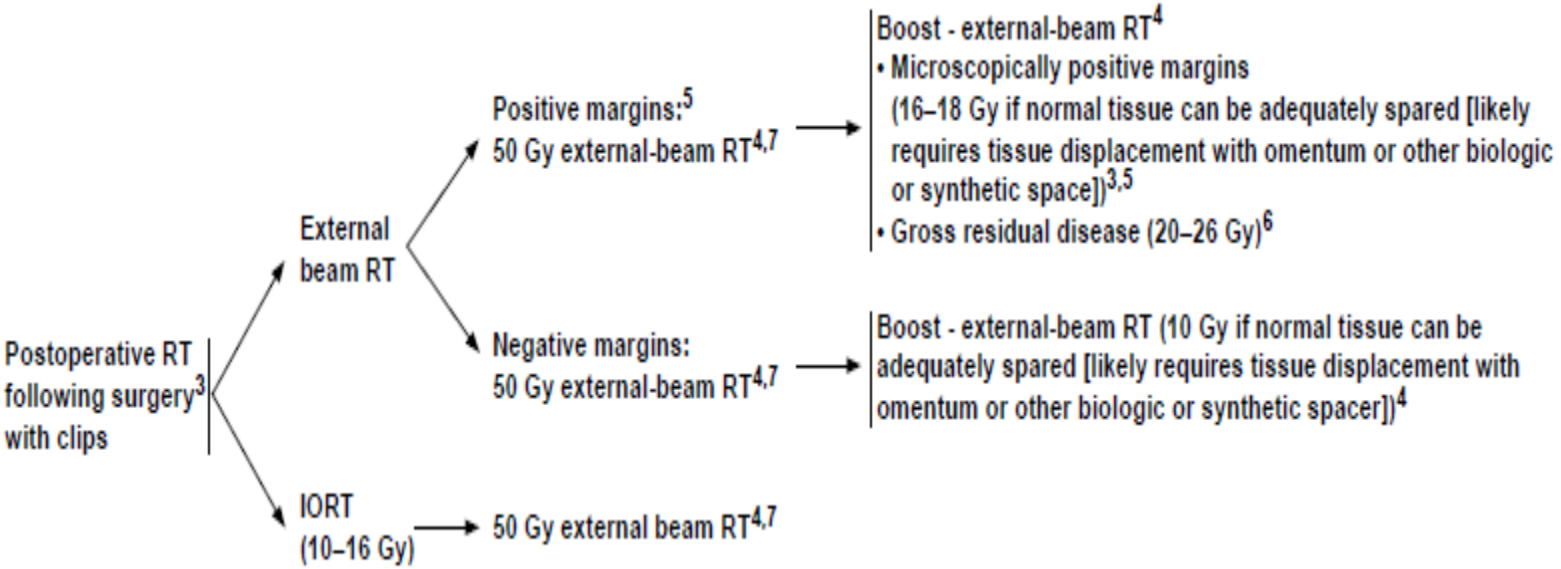



RADIATION THERAPY GUIDELINES FOR SOFT TISSUE SARCOMA OF EXTREMITY/TRUNK/HEAD-NECK[1,2]
Postoperative RT following surgery[3] with clips
External-beam RT[4,7] (50 Gy)
Boost Dose[4] (unless prior IORT)
Negative margins: 10–16 Gy EBRT[4,7]
Microscopically positive margins: 16–18 Gy[3,5]
Gross residual disease: 20–26 Gy[6]
IORT (10–16 Gy)
Brachy-therapy
Positive margins:[3]
• Brachytherapy
› Low-dose (16–20 Gy) or high-dose rate equivalent (14–16 Gy)
Clinical target volume (CTV):
• Total dose - 50 Gy external-beam RT[4]
Negative margins:
45 Gy low-dose rate brachytherapy or high-dose equivalent (ie, 36 Gy in 10 fractions of 3.6 Gy BID over 5 days)[8]

RADIATION THERAPY GUIDELINES FOR RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA[1]



RADIATION THERAPY GUIDELINES FOR RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA[10]



Chemotherapy

- Preoperative
- Postoperative
- Salvage
- Metastatic setting
- Targeted therapy

Adjuvant chemotherapy

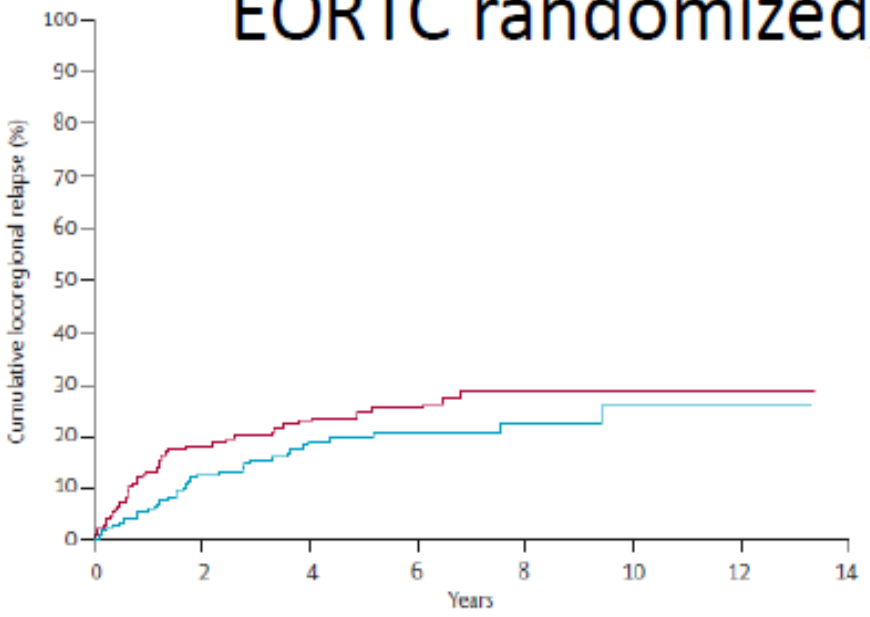
Study	details	Local	Distant	Over all	OS	Remarks
SMAC meta-analysis (2000) Median F/U 9.4years	14 RCTs 1564 patients Local STS Sx +/-RT Adj CT vs Obs	LRFI HR 0.73	For doxo based CT DRFI 0.70 Absolute benefit 6-10% 10years	Overall RFI HR 0.75	For doxo based CT OS HR 0.89 (NS) Absolute benefit 4% at 10yrs	Irrespective of grade/hp/RT
Pervaiz N et al (2008) Meta-analysis	18RCTS 1953 patients LSx +/-RT Adj CT vs Obs localised	OR 0.73	0.67	0.67	0.84 (all chemo) [NS] 0.56(Ifos +Doxo) (p value 0.01)	
Frustaci S et al 2001	RCT(n=60) Spindle cell sarcoma Doxo +Ifos vs Obs		DFS 48m vs 16 months		75 m vs 46m 19 % absolute benefit in 4yrs	89 m F/U 2003 5yr median survival 66% vs 46%
EORTC 62931 2007	RCT(n= high gr Doxo +I					
Le Cesne A et al 2014 F/U 8.5years	Pooled analysis of EORTC 62931 and SBSTG study (n=819)					Male/>40yrs/R1 Sx only better survival

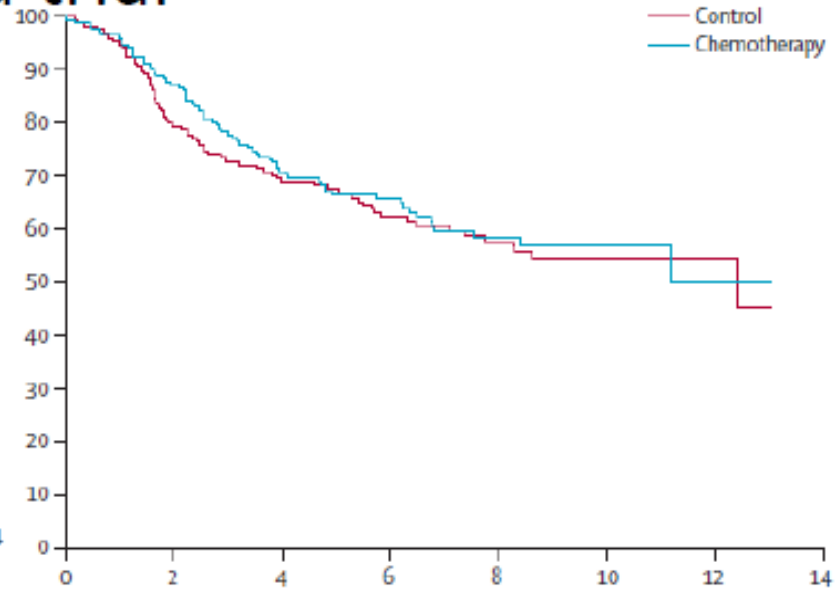
Category 2B recommendation n in STS adjuvant setting

Adjuvant chemotherapy

Outcome – impact of chemotherapy…less clear

EORTC randomized trial





Chemotherapy in advanced stage

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Soft Tissue Sarcoma

NCCN Guidelines Index
Soft Tissue Sarcoma, Table of Contents
Discussion

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES (NON-SPECIFIC)[a,b,c]

Soft Tissue Sarcoma Subtypes with Non-Specific Histologies[d,e]

Combination regimens

- AD (doxorubicin, dacarbazine)[1-4]
- AIM (doxorubicin, ifosfamide, mesna)[3-6]
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[3,4,7,8]
- Ifosfamide, epirubicin, mesna[9]
- Gemcitabine and docetaxel[10,11]
- Gemcitabine and vinorelbine[f,12]
- Gemcitabine and dacarbazine[13]

Single agents

- Doxorubicin[3,4,14]
- Ifosfamide[9,15]
- Epirubicin[16]
- Gemcitabine
- Dacarbazine
- Liposomal doxorubicin[17]
- Temozolomide[f,18]
- Vinorelbine[f,19]
- Pazopanib[f,g,20]
- Eribulin[f,21]
- Trabectedin[f,22,23,24]

GIST[h]

- Imatinib[25,26]
- Sunitinib[27]
- Regorafenib[28]

Disease progression after imatinib, sunitinib, and regorafenib

- Sorafenib[29-31]
- Nilotinib[32,33]
- Dasatinib[34] (for patients with D842V mutation)
- Pazopanib[35]

Desmoid Tumors (Aggressive fibromatosis)

- Sulindac[36] or other non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib
- Tamoxifen ± Sulindac[37,38]
- Toremifene[39]
- Methotrexate and vinblastine[40]
- Low-dose interferon[41]
- Doxorubicin-based regimens[42-44]
- Imatinib[45,46]
- Sorafenib[47]
- Methotrexate and vinorelbine[48]
- Liposomal doxorubicin[49]

Non-Pleomorphic Rhabdomyosarcoma

Combination regimens

- Vincristine, dactinomycin, cyclophosphamide[50]
- Vincristine, doxorubicin, cyclophosphamide[51]
- Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide[52]
- Vincristine, doxorubicin, ifosfamide[53]
- Cyclophosphamide and topotecan[54,55]
- Ifosfamide and doxorubicin[56]
- Ifosfamide and etoposide[57]
- Irinotecan and vincristine[58,59]
- Vincristine and dactinomycin[60]
- Carboplatin and etoposide[61]
- Vinorelbine[f] and low-dose cyclophosphamide[62]
- Vincristine, irinotecan,temozolomide[63]

Single agents

- Doxorubicin[64]
- Irinotecan[55,65]
- Topotecan[66]
- Vinorelbine[f,67]
- High-dose methotrexate[i,68]
- Trabectedin[f,22,23,24]

- For Soft Tissue Ewings, see NCCN Guidelines for Bone Cancer

Chemotherapy in advanced stage

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Soft Tissue Sarcoma

NCCN Guidelines Index
Soft Tissue Sarcoma, Table of Contents
Discussion

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA[a,c]

Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT)
- Imatinib[69]

Angiosarcoma
- Paclitaxel[70,71]
- Docetaxel
- Vinorelbine[f]
- Sorafenib[72]
- Sunitinib[73]
- Bevacizumab[74]
- All other systemic therapy options as per Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (SARC-E 1 of 6)

Solitary Fibrous Tumor/Hemangiopericytoma
- Bevacizumab and temozolomide[75]
- Sunitinib[76,77]

Alveolar Soft Part Sarcoma (ASPS)
- Sunitinib[78,79] (category 2B)

PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis
- Sirolimus[80-83]
- Everolimus[84]
- Temsirolimus[85,86]

Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation
- Crizotinib[87]
- Ceritinib[88]

Well-differentiated/Dedifferentiated Liposarcoma (WD-DDLS) for Retroperitoneal Sarcomas
- Palbociclib[89,90]

Un-resectable STS

- Primary RT (70-80Gy)
- Chemo RT
- Chemotherapy (Ifos + Doxo)
- Isolated Limb Perfusion(ILP)/Isolated Limb Infusion(ILI)

Limb perfusion: un-resectable extremity Sarcoma

- **ILP:**
- TNF alfa
- Melfalan
- Doxirubicin
- **ILI less invasive**

Table 4.3 ILP/TNF + mephalan in STS

Author	*Ref.*	*Year*	*Drug*	*No. of patients*	*% RR*	*% CR*
Vaglini	31	1994	TNF + melph	9	89	67
Gutman	23	1996	TNF + melph	35	94	37
Eggermont	8	1996	TNF/melph/IFN-γ	186	82	29

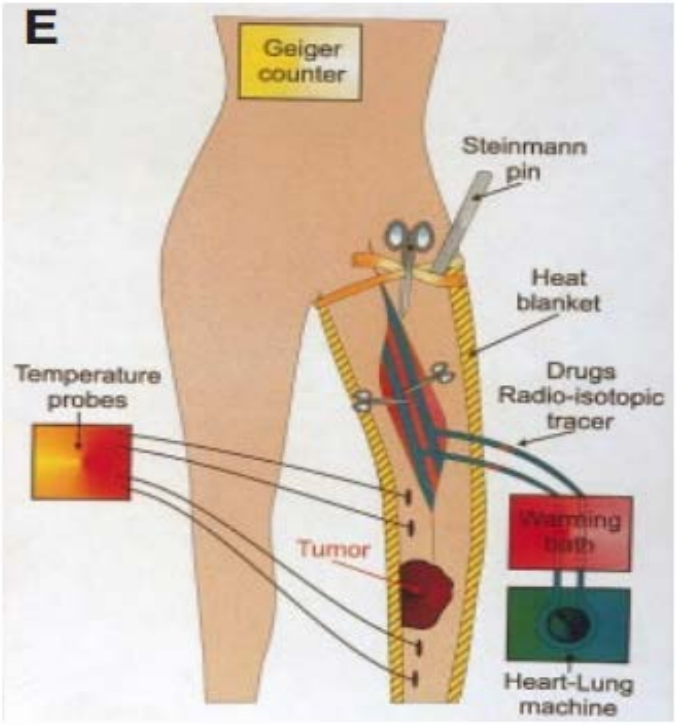


Figure 4.2 Isolated limb perfusion (ILP); stages of the procedure: **(A)** Entire limb is scrubbed, tissue thermistors are placed; **(B)** limb is wrapped with heating mattress; **(C)** wide exposure of the artery and vein, ligation of all the collaterals; **(D)** cannulation and proximal occlusion of blood vessels; **(E)** in iliac perfusions, a Steinman pin is inserted into the iliac bone to anchor the Esmark band.

Klauser JM et al. Sarcoma 2001

Pulmonary mets: Sarcoma

- 5yr survival 59% in LN mets and 9% in lung mets

Prognostic value:

- Synchronous lung mets
- Metastatectomy
- >4 pul. nodule