The Management of Soft Tissue Sarcomas

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Disclosure

• I have no conflicts of interest to disclose.
Learning Objectives

• Understand the biologic behavior of different histologic subtypes of sarcomas including response to radiation.
• Understand the rationale for the use of preoperative radiation in extremity and retroperitoneal soft tissue sarcomas.
• Understand the set up and clinical tumor volumes for treatment of extremity soft tissue sarcomas.
• Understand the set up and clinical tumor volumes for treatment of retroperitoneal soft tissue sarcomas.
• Appreciate the approach to patients with unplanned surgical excision of soft tissue sarcomas.
### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>220,800</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>115,610</td>
<td>105,780</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>69,050</td>
<td>63,610</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>56,320</td>
<td>54,870</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>42,890</td>
<td>47,230</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>39,850</td>
<td>32,000</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>38,270</td>
<td>31,200</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>32,670</td>
<td>24,120</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,900</td>
<td>23,370</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>25,510</td>
<td>23,290</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>848,250</strong></td>
<td><strong>810,170</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>86,380</td>
<td>71,660</td>
</tr>
<tr>
<td>Prostate</td>
<td>27,540</td>
<td>40,200</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>23,700</td>
<td>23,600</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,710</td>
<td>16,950</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>17,030</td>
<td>14,150</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,210</td>
<td>10,240</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,600</td>
<td>12,240</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,510</td>
<td>8,310</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,480</td>
<td>7,520</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>9,070</td>
<td>6,380</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>312,150</strong></td>
<td><strong>277,280</strong></td>
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</tbody>
</table>
Soft Tissue Sarcomas
Epidemiology

• 2015 estimated new cases of soft tissue cancers
  – 11,930  0.7% of all cancers

• 2015 estimated deaths from soft tissue cancers
  – 4,870  0.8% of all cancer deaths

CA A Cancer Journal 2015; 65: 5-29
### Soft Tissue Sarcomas

**Tumor Distribution**

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Thigh/buttock/groin</td>
<td>46%</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>13%</td>
</tr>
<tr>
<td>Torso</td>
<td>18%</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>13%</td>
</tr>
<tr>
<td>Head and neck</td>
<td>9%</td>
</tr>
</tbody>
</table>

Soft Tissue Sarcomas
Tumor Distribution

Soft Tissue Sarcomas

Pathology

• Sarcomas – heterogenous group of tumors arising from mesenchymal cells
  – > 100 different histopathologies
  – Diagnosis made on morphologic pattern with aid of immuohistochemical staining
  – Many have distinct chromosomal translocations
  – Many have implications for tumor location, behavior and treatment

Soft Tissue Sarcomas
Pathology

• Most common types:
  – Undifferentiated/unclassified sarcoma (pleomorphic/round cell/spindle cell)
  – Liposarcoma
  – Leiomyosarcoma
  – Synovial sarcoma
  – Malignant peripheral nerve sheath tumor (MPNST)
  – Rhabdomyosarcoma
  – Primitive neuroectodermal tumor (PNET) /extraskeletal Ewings
  – Angiosarcoma
  – Ephitheliod sarcoma
  – Clear cell sarcoma
  – Alveolar soft part sarcoma
  – Solitary fibrous tumors
Soft Tissue Sarcomas
Pathology

• Undifferentiated/unclassified STS: includes some ‘MFH’ ...category is for sarcomas that lack specific differentiation.

• Myxofibrosarcoma: previously called myxoid MFH
  – 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%)
Soft Tissue Sarcomas Pathology

- Liposarcoma – 4 distinct WHO subtypes
  - Well-differentiated/dedifferentiated LPS
  - Myxoid/round cell LPS
  - Pleomorphic LPS
  - Mixed

One of most common sarcomas: 13%
  - 24% of all extremity
  - 45% of RP sarcomas
Soft Tissue Sarcomas
Pathology

- Well-differentiated liposarcoma (WDLS)
  - Also known as atypical lipomatous tumors (ALT)
  - 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

Soft Tissue Sarcomas
Pathology

Atypical lipomatous tumor

Well-differentiated liposarcoma
Soft Tissue Sarcomas

Pathology

• Pleomorphic LPS – high rate of metastases; resemble undifferentiated – unclassified sarcomas

• Myxoid/Round cell LPS
  – Mean age in mid 40’s
  – Extremity in vast majority
  – Responsive to chemotherapy - trabectedin

**Round cell LPS**: component must be > 5%; high rate of metastases

**Myxoid LPS**: distant metastases – often to soft tissue sites, more than lung
Soft Tissue Sarcomas

Pathology

- 34 year old with growing posterior chest wall mass – told ‘lipoma’
- History revealed an old right thigh injury – larger appearing on exam
Soft Tissue Sarcomas
Pathology

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

Soft Tissue Sarcomas
Pathology

42 year old w enlarging right thigh mass

Prior to RT
17 x 11 x 6.7 cm

after RT
14 x 7.4 x 4.6 cm
Soft Tissue Sarcomas
Pathology

• **Leiomyosarcoma**
  – Can occur anywhere in the body, common in the retroperitoneum
  – Seen arising from vasculature – consider at surgery

• **Malignant peripheral nerve sheath tumors (MPNST)**
  – Originate from peripheral nerves
  – 50% occur in patients with NF type I
  – Most common in the extremities, trunk, H&N
Soft Tissue Sarcomas

Pathology

- **Epithelioid sarcomas**
  - Young adults
  - Upper extremity predilection – especially distal UE

- **Synovial sarcomas**
  - Originally thought to arise from the synovium of joints but actual origin is unknown
  - 2 types: monophasic and biphasic
  - Young adults
  - Histology that is more responsive to chemotherapy
Soft Tissue Sarcomas
Pathology

• Angiosarcomas
  – Uncommon
  – Arise in skin/subcutaneous tissue – most typically of the breast or H&N
  – One of most common sarcomas seen after RT
  – Chemoresponsive sarcoma- taxanes
Soft Tissue Sarcomas
Pathology

• Grade
  – usually a 3-tier system
  – Prognostic in some sarcomas
  – Some tumor types not typically graded
    • MPNST all felt to be high grade
    • Epithelioid
    • Clear cell sarcoma
    • Angiosarcoma
    • Extraskeletal myxoid chondrosarcoma
    • Synovial sarcoma

Soft Tissue Sarcomas
Clinical Presentation

• Extremity
  – Enlarging painless mass
  – Pain
  – Functional limitations
  – Symptoms associated with compression of local structures
Soft Tissue Sarcomas
Clinical Presentation

• Retroperitoneal
  – Abdominal mass – often incidentally found
  – Pain
  – Gastrointestinal: early satiety, obstruction, bleeding
  – Lymphedema, neurologic or musculoskeletal sx
Soft Tissue Sarcomas
Clinical Presentation

• Rare
  – Fevers/leukocytosis
  – Paraneoplastic hypoglycemia (leiomyosarcoma)
  – Symptoms from distant metastases
Soft Tissue Sarcomas
Pattern 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
Soft Tissue Sarcomas
Pattern 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

Soft Tissue Sarcomas
Pattern of Spread

• Retroperitoneal
  – Pushing/displacing adjacent organs
  – Enveloping structures
Soft Tissue Sarcomas Evaluation

• Extremity/trunk imaging
  – Plain radiography
  – MRI of primary site
  – (CXR)
  – CT chest
    • Add Abdomen/pelvis if tumor in groin/myxoid-round cell LPS
  – (PET)
Soft Tissue Sarcomas
Pattern of Spread

• Retroperitoneal
  – Hematogenous metastases – often late, if at all
    • Liver
    • Lung
Soft Tissue Sarcomas
Evaluation

• Retroperitoneal
  – CT abdomen/pelvis
  – (CXR)
  – CT chest
  – (MRI)
  – (PET)
Soft Tissue Sarcomas Evaluation

• Biopsy:
  – FNA
  – Core needle biopsy – multiple samples
    • Site of biopsy is important for representative sample
    • CT/ultrasound guidance
  – Incisional biopsy – if needed (extremity)
    • Ideally by surgeon who will do definitive surgery
    • Longitudinal in extremity
    • Adequate hemostasis
Soft Tissue Sarcomas Team

• Treatment requires input from team
  – Radiologist (biopsy/organs/structures involved)
  – Pathologist (grade/tumor type)
  – Surgeon(s) (orthopedic/general/plastics/vascular)
  – Medical oncologist
  – Radiation oncologist
Soft Tissue Sarcomas
Team Approach - Extremity

• Surgical resectability issues
  – Vascular involvement
  – Joint involvement
  – Tissue planes - adjacency to bone
  – Functional loss
  – Need for plastic surgery/hand surgeon
Soft Tissue Sarcomas
Team Approach - Extremity

- Radiation issues
  - Can the patient lie still?
  - Extremity: can a stripe of normal tissue be spared?
  - What surgical issues will impact the radiation?
    - What will be removed?
  - Should radiation be preoperative or postoperative?
Soft Tissue Sarcomas
Treatment Issues - Extremity

1994-97 Toronto Randomized Trial
Pre vs Postoperative RT Extremity

Endpoint: acute wound complications
Defined: second operation or extended non-surgical wound care

<table>
<thead>
<tr>
<th>Dose</th>
<th>All Complic’ns</th>
<th>Thigh</th>
<th>Skin toxicity</th>
</tr>
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<tbody>
<tr>
<td>Preop 50 Gy/25</td>
<td>35%</td>
<td>45%</td>
<td>32/88</td>
</tr>
<tr>
<td>Postop 66 Gy/33</td>
<td>17%</td>
<td>28%</td>
<td>64/94</td>
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p = 0.01
p<0.0001
Soft Tissue Sarcomas
Treatment Issues - Extremity

Toronto Randomized Trial
Long-term evaluation

<table>
<thead>
<tr>
<th>Grade &gt; 2</th>
<th>Pre-Op</th>
<th>Post-Op</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>31.5%</td>
<td>48.2%</td>
<td>0.07</td>
</tr>
<tr>
<td>Edema</td>
<td>15.1%</td>
<td>23.2%</td>
<td>ns</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>17.8%</td>
<td>23.2%</td>
<td></td>
</tr>
</tbody>
</table>

Davis AM Radiother Oncol. 205;75:48-53.
Soft Tissue Sarcomas
Treatment Issues - Extremity

Toronto Randomized Trial: Long-term evaluation

MSTS & TESS functional scores
- lower with grade ≥ 2 fibrosis \( p < 0.002 \)
- lower with grade ≥ 2 joint stiffness \( p = 0.001 \)
- lower with grade ≥ 2 edema \( p < 0.01 \)

Field size (treatment volume): only risk factor for
- increased fibrosis \( p = 0.002 \)
- joint stiffness \( p = 0.006 \)
- marginally of edema \( p = 0.06 \)

Davis AM Radiother Oncol. 205;75:48-53.
Soft Tissue Sarcomas
Treatment Issues - Extremity

Simulation: Customized immobilization
- Proximal extremity
  - ST motion
  - skin folds
  - genitalia
  - distance of arm to head
Soft Tissue Sarcomas
Treatment Issues - Extremity

• Distal extremity - fixation to prevent rotation and move other limb out.
Soft Tissue Sarcomas
Treatment Issues - Extremity

- Mid extremity – let tissue be dependent if possible
Soft Tissue Sarcomas
Treatment Issues - Extremity

- 1970’s-1980’s – 10 cm margins (5 cm for low grade)
- 1990’s – NCIC study used 5 cm margins
  - Histologic data showed MRI signal 0-7.1 cm, mean 2.5
  - Tumor cells seen in 10/15 cases most within 1 cm but up to 4 cm from mass
  - Presence of tumor cells not correlate with edema/tumor size

Soft Tissue Sarcomas

Treatment Issues - Extremity

Target volume definitions for preoperative 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

Soft Tissue Sarcomas
Treatment Issues - Extremity
Soft Tissue Sarcomas
Treatment Issues - Extremity

Target volume definitions for postoperative RT

• CTV: shrinking field technique

Initial volume

– Surgical bed reconstructed from preop imaging
  • Fusion of preop 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

Soft Tissue Sarcomas
Treatment Issues - Extremity

Target volume definitions for postoperative RT

• CTV: shrinking field technique

Boost volume
  – Same as initial volume except in the longitudinal
  – Use GTV reconstructed with 2 cm margins

• Other issue: scar/drain site
  – Historically included
  – Low risk situations, drain site could be omitted

Soft Tissue Sarcomas
Treatment Issues - Extremity
Soft Tissue Sarcomas
Treatment Issues - Extremity

• Local control related to fields
  LR patients had significantly
  higher grade
  margin positive
  recurrent disease
  more postoperative boost patients
  slightly older
  more shoulder relapses

Soft Tissue Sarcomas

Treatment Issues - Extremity

- Local control related to fields
  - Evaluation of recurrence site

  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

- Second report: 68% (17/20) in-field
  16% (4/20) out-of-field
  16% (4/20) marginal

Soft Tissue Sarcomas
Treatment Issues - Extremity

Unplanned excision: common phenomena
– Typically smaller
– Typically subcutaneous (mistaken for lipomas)
– Often low grade

Residual disease 24-74%

Soft Tissue Sarcomas
Treatment Issues - Extremity

How does inadvertent excision affect outcome/treatment?
- Re-excision is the norm...to obtain negative margins
- Inappropriate skin incision common
- Controlled studies – mostly show similar local control and survival to those with primary management
- Rate of use of radiation is higher
- Higher rate of more aggressive surgery (amputation)-leading to poorer functional outcome

Soft Tissue Sarcomas
Treatment Issues - Extremity

IMRT in extremity STS

• 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)

Use: upper thigh – most to gain
Soft Tissue Sarcomas
Treatment Issues - Extremity

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

Use of IMRT with IGRT

Wound complications 30.5% (43% rand trial)
Primary closure 93.2% (71.4%)*
Flap $\geq$ 30 Gy 62.7% (69.8%)*

Trend – higher mean dose to skin flaps in WC pts

*significant

Soft Tissue Sarcomas
Treatment Issues - Extremity
Outcome – local control – excellent >90% at 3-5 yrs

Local recurrence
Logrank p=0.7119

Proportion event-free (%)

Preoperative radiotherapy
Postoperative radiotherapy

Local disease-free survival
Low grade
High grade n = 1814

n = 2934

P = 0.009

Probability

Years

P < 0.0001
Soft Tissue Sarcomas
Treatment Issues - Extremity

Outcome – impact of chemotherapy...less clear

Local Control

Overall Survival
Soft Tissue Sarcomas
Treatment Issues - Extremity

Outcome – impact of chemotherapy...less clear

EORTC randomized trial
Soft Tissue Sarcomas
Team Approach - Retroperitoneal

• Surgical resectability issues
  – Resectable to R0
  – Vascular involvement
  – Organ involvement
  – Functional loss
  – Need for vascular or other surgical specialty
Soft Tissue Sarcomas
Team Approach - Retroperitoneal

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

Soft Tissue Sarcomas
Treatment Issues - Retroperitoneal

- To treat or not to treat?
  Postoperative RT
    Rarely can achieve adequate dose
    More gastrointestinal toxic
  Preoperative RT
    Advantages
      tumor readily identifiable
      tumor displaces bowel
      potential tumor reduction
      pseudocapsule formation/margin improvement
      typically a lower dose is felt to be needed
- EORTC 62092: evaluating preoperative RT

Soft Tissue Sarcomas
Treatment Issues - Retroperitoneal

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

Soft Tissue Sarcomas
Treatment Issues - Retroperitoneal

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

Soft Tissue Sarcomas
Treatment Issues - Retroperitoneal

- Dose escalation areas of high risk
  - IORT/IOHDR – challenging due to size/toxicity
  - Brachytherapy - toxicity high
  - Concurrent boost with IMRT
    Defined margin risk area/meeting constraints to bowel
- Belgium study – only treated the posterior border of tumor
- U Ab study – SIB to 57.5 Gy

Treatment was tolerated well
Numbers too small and too short of FUP to know impact
Soft Tissue Sarcomas
Treatment Issues - Retroperitoneal

Outcome – significantly worse than other sites
- Local disease free survival
- Disease specific survival
Soft Tissue Sarcomas
Treatment Issues - Retroperitoneal

- Outcome – not as good
MSKCC series of >1000 pts

- Outcome – may be influenced by where tx is given single tertiary vs multicenter group

Dutch study 5 yr OS
Low grade  89 vs 68%
High grade  40 vs 46%
Key Points to Take Home

1. Soft tissue sarcomas are not one but multiple different tumors, each with special characteristics that need to help mold the treatment and influence the patient outcome.

2. Most extremity soft tissue sarcomas rarely involve lymph nodes and primarily metastasize to the lungs. Know the ‘exception’ sarcomas.

3. Appreciate and be able to interact with other team members in the management of soft tissue sarcomas.

4. Preoperative radiation in extremity lesions reduces volume and dose of radiation with equal local control and less long term toxicity/better functional outcome.

5. Understand the approach to patients with unplanned surgical excision of soft tissue sarcomas.

6. Be able to describe the appropriate clinical tumor volumes in preoperative extremity and retroperitoneal soft tissue sarcomas.