Radiation Therapy for Soft Tissue Sarcomas

JOHN P. HAYES, MD
NORTHWESTERN UNIVERSITY
What Are Sarcomas?

- Sarcomas are malignancies that arise from:
  - Bone
  - Muscle
  - Fat
  - Tendons
  - Ligaments
  - Blood Vessels (but not blood or lymphatic malignancies)
  - Nerves and nerve coverings
- These are the support tissues of the body

And there are multiple different cells that make up these tissues.
Characteristics of Sarcomas

Sarcomas comprise approximately 1% of all adult malignancies

- Approximately 80% are soft tissue malignancies
  - Rhabdomyosarcomas (striated muscle)
  - Leiomyosarcomas (smooth muscle)
  - Liposarcoma (fat)
  - Angiosarcoma (blood vessel)

- Approximately 20% are malignancies of the bone
  - Osteosarcoma (bone)
  - Ewing’s Sarcoma (bone)
  - Chondrosarcoma (cartilage)
Characteristics of Sarcomas

- The frequencies of the various types of soft tissues sarcoma vary by time and region of the world studied.
- Leiomyosarcoma was the most frequent subtype in a study of 9 SEER program studies of over 26,000 cases between 1978 and 2001.
What Causes Sarcomas?

Genetic syndromes linked to sarcoma development:

- Li-Fraumeni (*TP53* mutation)
- retinoblastoma (*RB1* gene deletion)
- neurofibromatosis type-1 (*NF1* mutation)
- Gardner (*APC* mutation)
- McCune-Albright syndrome (*GNAS1* mutation)
- Bloom, Rothmund-Thomson, and Werner syndromes (associated with loss of helicase function)
What Causes Sarcomas?

- Cause vs Association
- Environmental exposures
  - Vinyl chloride (hepatic angiosarcoma)
  - Dioxins or phenoxyacetic acid herbicides such as Agent Orange
  - Radiation exposure (including therapeutic radiation)
- Lymphedema (Stewart-Treves syndrome: lymph-angiosarcoma)
- Viruses (human herpesvirus 8 and Kaposi sarcoma)

Trauma is not thought to be a cause of sarcomas.
## What Causes Sarcomas?

### Representative Genetic Alterations in Sarcomas

<table>
<thead>
<tr>
<th>Class of Alteration</th>
<th>Sarcoma Subtype</th>
<th>Genetic Change</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating mutation</td>
<td>Gastrointestinal stromal tumor</td>
<td>KIT or PDGFRA mutation</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Ligand expression</td>
<td>Dermatofibrosarcoma protuberans</td>
<td>PDGF expression</td>
<td>~100%</td>
</tr>
<tr>
<td></td>
<td>Giant cell tumor of the bone</td>
<td>RANK ligand</td>
<td>~100%</td>
</tr>
<tr>
<td>Inactivation / deletion</td>
<td>Myxofibrosarcoma Malignant peripheral nerve sheath</td>
<td>NF1 mutation NF1 deletion</td>
<td>~10% to 20 % &gt;90 %</td>
</tr>
<tr>
<td>Gene amplification</td>
<td>Well-differentiated and dedifferentiated liposarcoma</td>
<td>CDK4, MDM2 amplification</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Translocation</td>
<td>Synovial sarcoma</td>
<td>t(18;X) SYT-SSX1 or SYT-SSX2</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td></td>
<td>Ewing sarcoma</td>
<td>t(11;22) EWSR1-FLI1</td>
<td>&gt;85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(21;22) EWSR1-ERG</td>
<td>5% to 10%</td>
</tr>
<tr>
<td></td>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13) PAX3-FOX01</td>
<td>~70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(1;13) PAX7-FOX01</td>
<td>~15%</td>
</tr>
</tbody>
</table>
How Are Sarcomas Diagnosed?

- Common presenting symptoms include:
  - Enlarging mass
  - Most commonly a painless enlarging mass, local discomfort can occur
  - Site-specific symptoms:
    - Cramping (bowel obstruction)
    - Shortness of breath (thoracic mass)
    - Dysfunction of an extremity (nerve or joint lesions)
  - Metastatic disease
    - Pain (bone metastases)
    - SOB (lung metastases)

Patients are often without symptoms. That is, their tumors are discovered incidentally.
How Are Sarcomas Diagnosed?

Tissue Is the Issue!

- Needle biopsy
  - Core
  - Fine needle (FNA) [generally inadequate]
- Incisional biopsy (planned vs “accidental”)
- Excisional biopsy (“accidental”)

Plan well!
What Treatment Is Best?

First Things First! - Staging

Evaluate

- Primary disease
- Distant disease
- Lymphatic involvement
  - Rhabdomyosarcoma
  - Angiosarcoma
  - Clear Cell sarcoma
  - Epithelioid sarcoma
  - Synovial sarcoma
Staging – The Primary Tumor

MRI
Staging – Metastatic Disease

- Distant metastases
  - Lung
  - Bone
  - Brain
  - Liver
Staging

PET/CT
What is the Best Treatment?

Considerations include:

- Location
- Stage (extent of disease)
- Cell type
- Grade
- Previous treatment
  - Biopsy
  - Excision
Sarcoma Treatments

- Surgery
- Radiation Therapy
- Systemic Therapies

“Local Treatments”

“Whole Body Treatment”
Radiation Therapy for Sarcomas

Radiation Therapy is the use of various forms of energy delivered to malignant tissues with a result that can lead to the death of the malignant cells.
Radiation Is Energy!
Radiation Therapy for Sarcomas

- Neoadjuvant radiation therapy
- Adjuvant radiation therapy
- Radiation therapy for unresectable disease
- Radiation therapy for metastatic disease
  - Ablative therapy for salvage
  - Palliative treatments
How is Radiation Therapy Given?

- External Beam Radiation Therapy (EBRT)
  - Three-dimensional Conformal Radiation Therapy (3DCRT)
  - Intensity Modulated Radiation Therapy (IMRT)
  - Image-Guided Radiation Therapy (IGRT)
  - Proton Beam Therapy
Radiation Therapy Planning

Simulation:
Radiation Therapy
Radiation Therapy Planning
Image Guided Radiation Therapy (IGRT)

Linear Accelerator + CT Scanner
Image Guided Radiation Therapy (IGRT)
Image Guided Radiation Therapy (IGRT)
Radiation Therapy for Sarcomas

Neoadjuvant Radiation Therapy:
- Improve local control
  - “Deep” tumors
  - > 5 cm
  - High grade
- Improve function (including limb preservation)
- Increase the likelihood of resection
- Improve rate of negative margins

Adjuvant Radiation Therapy:
- Improve local control
  - “Deep” tumors
  - > 5 cm
  - High grade
- Improve function (including of limb preservation)
- Address incomplete resections
  - Positive microscopic margins
  - Gross residual disease
Radiation Therapy for Sarcomas

- Advantages of pre-operative treatment (neoadjuvant treatment):
  - Generally require smaller volumes
  - The dose is approximately 20% less
  - Coordination with surgery
  - Functional outcome may be better for extremity sarcoma (especially proximal extremities)

- Disadvantages of pre-operative treatment (neoadjuvant RT):
  - Wound healing complications
  - Final pathology characteristics may be different
Stereotactic Body Radiation Therapy (SBRT):
- Image guided
- High dose, short duration

Goals
- Ablative therapy -
  (limited number of metastases = “oligometastases”)
- Palliation (insensitive tumor types)
Radiation Therapy for Sarcomas

Stereotactic Body Radiation Therapy (SBRT)
Radiation Therapy for Sarcomas

Stereotactic Body Radiation Therapy (SBRT)
The energy that is imparted by a beam of radiation is dependent on its energy and mass.
Proton Vs. Photon Therapy - Physics

THE BRAGG PEAK

www.isrealprotontherapy.com
Proton Beam Therapy for Sarcoma
Northwestern Medicine Chicago Proton Center
Proton Beam Therapy

Protons as compared to photons:

- Protons are positively charged particles with a relatively large mass
- Protons impart their energy over a much smaller distance
- Shaping of the distribution of proton energy requires spreading out the area of absorption into the tissues
- Little if any exit dose (dose beyond the target)
- *Can have* to a spatial advantage in the distribution of energy
- *May have* a biologic disadvantage

- Photons are uncharged particles with no mass
- Photons impart their energy over a longer distance
- Shaping is accomplished by combining different beams (angles and sizes) along with filtering of beams
- The energy can be tightly confined to irregular target volumes, however, this leads to lower doses being spread out to surrounding tissues

*At what cost?*
Important Questions:

- How much dose is needed?
- What are the normal tissues nearby? (i.e. critical structures or organs at risk?)
- Is there target motion? How does that change things?
- What are the risks of photon beam radiation therapy? Can these risks be significantly reduced?
- Is surgery planned? Coordination with the surgeon?

Is it covered by my insurance?
The “Best” Radiation Therapy

- Fits the clinical situation - *One size does not fit all!*
- Factors in other considerations:
  - medical issues
  - age
- Works cooperatively with other forms of therapy (i.e. understands the roles of surgery and systemic agents)
- Follows *“Hayes’ Rules”*
  - *Hit what you need to hit*
  - *Miss what you need to miss*
- Understands the limits of technology