What’s New in Orthopedic Oncology

Nader A. Nassif M.D.
OrthoCalifornia
Hoag Orthopedic Institute
Hoag Family Cancer Institute

I have no financial Disclosures
Outline

• New innovations in diagnosis in Orthopedic Oncology

• Surgical Management of Soft Tissue Sarcoma
  – Soft tissue Margin Assessment

• Surgical Management of Bone Sarcoma
  – 3D Navigation
  – Custom Jigs
  – 3D Printed Implants/tumors for planning

• Metastatic disease
Soft Tissue Sarcoma Epidemiology

- 12,000 cases per year diagnosed
- 3.2/100,000
- < 1% of all new cancer diagnoses
- Men > Women (1.42:1)
Soft Tissue Sarcoma Epidemiology

• Age:
  – Mostly Adults with some exceptions
  – 15% younger than 15 yo
  – 40% older than 55 yo

• Location
  – 60% extremity
  – 20% trunk
  – 20% retroperitoneum, head and neck
Bone Sarcoma Epidemiology

• Malignant: 2,500 cases per year 30-40% mortality
## Primary Bone Tumors

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>Metastatic Neuroblastoma, Rhabdomyosarcoma</td>
</tr>
<tr>
<td>5-20</td>
<td>Osteogenic Sarcoma; Ewing’s and Chondroblastoma</td>
</tr>
<tr>
<td>20-30</td>
<td>Giant Cell Tumor</td>
</tr>
<tr>
<td>30+</td>
<td>Chondrosarcoma &amp; Soft Tissue Sarcoma</td>
</tr>
<tr>
<td>60+</td>
<td>Metastatic Carcinoma, Multiple Myeloma, Lymphoma</td>
</tr>
</tbody>
</table>
# Primary Bone Tumor location

<table>
<thead>
<tr>
<th>Location</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiphysis</td>
<td>Chondroblastoma (Immature)</td>
</tr>
<tr>
<td></td>
<td>Giant Cell Tumor (Mature)</td>
</tr>
<tr>
<td>Metaphysis</td>
<td>Osteogenic Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Diaphysis</td>
<td>Ewing’s Sarcoma,</td>
</tr>
<tr>
<td></td>
<td>Adamantinoma (Tibia)</td>
</tr>
<tr>
<td>Flat Bones</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td></td>
<td>Ewing’s Sarcoma</td>
</tr>
<tr>
<td>Paraosteal</td>
<td>Osteogenic Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Chondroma</td>
</tr>
</tbody>
</table>
Sarcoma!
# Genetic Translocations

<table>
<thead>
<tr>
<th>Sarcoma Type</th>
<th>Chromosomal Translocation</th>
<th>Fusion Gene</th>
<th>Year Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing sarcoma</td>
<td>t(11;22)(q24;q12)</td>
<td>EWS-FLI1</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>t(21;22)(q22;q12)</td>
<td>EWS-ERG</td>
<td>1993</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWS-ATF1</td>
<td>1993</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(11;22)(p13;112)</td>
<td>EWS-WT1</td>
<td>1994</td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;22)(q22;q12)</td>
<td>EWS-CHN</td>
<td>1995</td>
</tr>
<tr>
<td>Myxoid/round cell liposarcoma</td>
<td>t(12;16)(q13;p11)</td>
<td>TLS-CHOP</td>
<td>1993</td>
</tr>
<tr>
<td>Angiomyxoid fibrous histiocytoma</td>
<td>t(12;16)(q13;p11)</td>
<td>TLS-ATF1</td>
<td>2000</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13)(q35;q14)</td>
<td>PAX3-FKHR</td>
<td>1993</td>
</tr>
<tr>
<td></td>
<td>t(1;13)(p36;q14)</td>
<td>PAX7-FKHR</td>
<td>1994</td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;17)(q22;q11)</td>
<td>TAF2N-CHN</td>
<td>1999</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(X;18)(p11;q11)</td>
<td>SYT-SSX1,2</td>
<td>1994</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>t(17;22)(q22;q13)</td>
<td>COL1A1-PDGFB</td>
<td>1997</td>
</tr>
<tr>
<td>Congenital fibrosarcoma</td>
<td>t(12;15)(p13;q25)</td>
<td>ETV6-NTRK3</td>
<td>1998</td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>t(2p23)</td>
<td>Various ALK</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fusions</td>
<td></td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>t(X;17)(p11;q25)</td>
<td>ASPL-TFE3</td>
<td>2001</td>
</tr>
<tr>
<td>Endometrial stromal sarcoma</td>
<td>t(7;17)(p15;q21)</td>
<td>JAZF1-JJAZ1</td>
<td>2001</td>
</tr>
</tbody>
</table>
Genetic Markers For Diagnosis

• MDM-2 - Liposarcoma
• STAT-6 - Solitary Fibrous Tumor
• TLE-1 - Synovial Sarcoma
• TFE-3 - Aleolar Sarcoma of Soft parts
• INI-1 - Epitheiloid Sarcoma
• Sox-10
Genetic Markers for Diagnosis

- MDM-2/CDK 4 - Osteogenic Sarcoma
- CD 99/O-13 - Ewing’s Sarcoma
- FGFR-23 - Fibrous dysplasia
- H3F3 - ABC
Diagnostics

• Increasing reliance on Genomic Analysis
**About the Test:**
FoundationOne® Heres is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

**Patient Information**
- **Patient Name:** Not Given
- **Date of Birth:** Not Given
- **Sex:** Not Given
- **FIM Case #:** 000000/111
- **Medical Record #:** 6
- **Specimen ID:** Not Given
- **Medical Facility ID:** -1

**Tumor Type:** Bone Marrow Multiple Myeloma

**Specimen Received:** Not Given
**Specimen Site:** Not Given
**Date of Collection:** Not Given
**Specimen Type:** Bone Marrow
**Extracellular DNA + Extracted RNA:** Not Given

**Patient Results**
- **6 Genomic Alterations**
- **4 Therapies Associated with Potential Clinical Benefit**
- **0 Therapies Associated with Lack of Response**
- **15 Clinical Trials**

**Genomic Alterations Identified**
- **KRAS G86H**
- **MTOR D2912Y**
- **IGHV-IGH-MAF rearrangement**
- **NTRK3 UBE2R2-NTRK3 fusion**
- **TRAF3 S84***
- **CXCR4 S323I rs25**

**Therapeutic Implications**

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient's tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS G86H</strong></td>
<td>None</td>
<td>Idealisib, Trametinib</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>MTOR D2912Y</strong></td>
<td>None</td>
<td>Everolimus, Temsirolimus</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>IGHV-IGH-MAF rearrangement</strong></td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>NTRK3 UBE2R2-NTRK3 fusion</strong></td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>TRAF3 S84</strong>*</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td><strong>CXCR4 S323I rs25</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Soft Tissue Sarcoma: Treatment

• Surgery

• Radiation

• Chemotherapy
Surgical Treatment of STS

• Biopsy
  – paramount importance
  – Important to discuss technique and location with orthopedic oncologist to ensure appropriate location and orientation
Surgical Management

• Wide Resection
• Dead space management
• Soft tissue coverage if necessary
New Drugs for Benign Disease

• Giant Cell Tumor of Bone - Denosumab

• Giant Cell Tumor of Tendon sheath - CSF-1R Kinase Inhibitor
Giant Cell Tumor of Bone

Denosumab - rank-L inhibitor

- Phase II Clinical Trials
  - 86% response rate
    - 48% - avoided surgery
    - 38% - downstaged surgery
  - 120 mg SC qmonth

Rutkowski et al Ann Surg Onc Sept 2015
Concerns regarding Denosumab

• Possible malignant transformation?

• Treated bone demonstrated morphologic overlap with malignant GCT

PVNS/GCT of Tendon sheath

• CSF-1R Kinase Inhibitor Trials
  – Phase 2: 38 pts, median 12 mo, min 6 months
  – Results (out of 25):
    • 1 metastatic disease (4%)
    • 3 progressive disease (12%)
    • 5 stable disease (20%)
    • 12 partial response (48%)
    • 0 complete response

Tap et al. J Clin Onc Vol 32 No 15. suppl May 2014
Healey et AL. MSTS/ISOLS 2015
Surgical Reconstructions

• Custom cutting blocks
• 3D printing
• Infection Resistant implants
Custom Cutting Blocks

- CT/MRI Registration
- Alternative to Intraoperative navigation
- 3D Printed custom guides for tumor and allograft
On the Horizon: 3D Printed Implants

• 3D Printing Technology is improving at a rapid rate
• Printing Metal implants with a high degree of complexity is feasible.
Infection Resistant Implants

• Silver Coated Implants
  – Not FDA approved in the US yet
  – Promising Preliminary results
    • 2% vs 10.5% in retrospective study for 158 pts
    • 11 vs 22% in retrospective study of 170 pts

Albergo et al Paper 65 ISOLS 2015
Donati et al Orthopedic Proceeding May 2016