Sarcoma Updates and New Approaches

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Disclosures

Nothing relevant to report
Objectives

- Background—overview and classification of sarcomas
- Randomized control trials in the management of STS
- Areas of evolving care—looking ahead at individualized care
Background—the challenge

> 50 types of sarcomas

Molecular footprint

**Genetic mutations in sporadic STS**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-diff/dediff LPS</td>
<td>MDM2 and CDK4 mutation</td>
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<tr>
<td>Myxoid/round cell LPS</td>
<td>FUS-CHOP translocation</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>SSX-SYT translocation</td>
</tr>
<tr>
<td>GIST</td>
<td>C-kit overexpression</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Myc amplification</td>
</tr>
<tr>
<td>DFSP</td>
<td>COLA1-PDGF fusion</td>
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<tr>
<td>Desmoid tumor</td>
<td>CTNNB1 mutation</td>
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<tr>
<td>Epithelioid hemangioendothelioma</td>
<td>WWTR1-CAMTA1 fusion</td>
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</tbody>
</table>

Crago and Singer, ACS Surgery.
Background—the challenge

75-100 types of sarcomas

Molecular footprint

<table>
<thead>
<tr>
<th>Hystology</th>
<th>Chromosome alteration</th>
<th>Fusion gene/gene alteration</th>
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<tbody>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>KK(17p11.21p11)</td>
<td>ASPL-GTER</td>
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<tr>
<td>Clear cell sarcoma</td>
<td>K(12,23)(q13,13)</td>
<td>EWS1-ATF1</td>
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<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>K(7,22)(p22,q13)</td>
<td>COL1A1-ROSFB</td>
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<tr>
<td>Endometrial stromal sarcoma</td>
<td>K(7,17)(p15q21)</td>
<td>JAZF1-SUZ12, JAZF1-PP1</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>K(22)q12</td>
<td>EFCRAB1</td>
</tr>
<tr>
<td>Epithelioid hemangiendothelioma</td>
<td>K(2,3)(p25,q26)</td>
<td>WWT1-GAMT1</td>
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<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>K(9,22)(q22q13)</td>
<td>ENPP1-NR4D3</td>
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<tr>
<td>Fetalcaudal myxoid chondrosarcoma</td>
<td>K(9,13)(q34q34)</td>
<td>TCHCR-NR4D3</td>
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<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>K(1,22)(p11q12)</td>
<td>TRIM32-AUX</td>
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<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td>K(7,16)(p11q13)</td>
<td>FUS-CREBL2</td>
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<tr>
<td>Myxoid (round cell) liposarcoma</td>
<td>K(1,21)(p13q11)</td>
<td>FUS-CREBL1</td>
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<tr>
<td>PeComa</td>
<td>K(1,21)(p13q11)</td>
<td>TR3 rearrangement</td>
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<tr>
<td>Salivary fibrous tumor</td>
<td>Chr12q21.3 inversion</td>
<td>MYBL2-STAT5B</td>
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<tr>
<td>Synovial sarcoma</td>
<td>K(5,16)(p11q11)</td>
<td>SS18-DDIT3</td>
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<tr>
<td>Well-differentiated liposarcoma and typical liposarcoma</td>
<td>Chr12q14-q15 amplification</td>
<td>MDM2, C0X4 amplification</td>
</tr>
</tbody>
</table>

Two broad categories of sarcomas

- Complex karyotype with peculiar cytogenetic transformations:
  - SSX-SYT in synovial sarcoma
  - FUS-DDTR in myxoid/round cell LPS

- Simple karyotype with specific genetic mutations:
  - MDM2 in well-differentiated LPS
  - c-KIT in GIST
Background—Soft tissue sarcomas

**Incidence:**
- Mesenchymal in origin
- 11,000 cases (<1% of all adult cancers)
- 3,500 deaths

**Risk factors:**
- majority sporadic
- radiation exposure
- chronic lymphedema

**Prognostic factors:**
- Size
- Grade
- Depth
- Margin status

**Anatomic distribution**

- Lower Extremity: 29%
- Visceral: 21%
- Upper Extremity: 12%
- Retro / IA: 16%
- Trunk: 10%
- Other: 12%

**Background--Predominant Histopathology by Site**

- Fibrosarcoma
- Leiomyosarcoma
- Liposarcoma
- MPNST
- MFH
- Myxofibrosarcoma
- Synovial

**Courtesy of Dr. Murray Brennan**

MSKCC 7/1/82 -12/31/08  n = 8003
Management of sarcomas

Basic tenets of multimodality therapy for extremity sarcomas

- Surgery: limb-sparing resection
- Radiation: deep, tumor size > 5 cm, high-grade
- Chemotherapy: ???

Limb-sparing surgery +/- radiation

Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjuvant Chemotherapy

Steven A. Rosenberg, M.D., Ph.D.,* Joel Tepper, M.D.,† Eli Glatstein, M.D.,† Jose Costa, M.D.,† Alan Baker, M.D.,* Murray Brennan, M.D.,* Ernest V. DiMoss, M.D.,* Claudia Sepp, R.N.,* William F. Sin德尔, M.D., Ph.D.,* Paul Sugarbaker, M.D.,* Robert Wesley, Ph.D.§

Summary #1

• Limb sparing resection for extremity sarcomas yields equivalent results to radical (amputation) surgery with respect to disease free survival and overall survival.

• Radiation reduces the incidence of local recurrence but does not result in a reduction of disease-specific or overall mortality.

• Regional therapies can influence regional outcomes, but regional disease does not typically result in mortality and tumor biology overwhelmingly appears to impact overall prognosis.

Retroperitoneal sarcomas

EORTC Soft Tissue and Bone Sarcoma Group
EORTC Radiation Oncology Group

A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with Retroperitoneal sarcoma (RPS)

EORTC protocol 62092-22092
STRASS
Chemotherapy for sarcoma

**Trials 1980-2000s**
- overall, conventional cytotoxic chemotherapy has shown limited efficacy in soft tissue sarcomas.
- *peculiar chemosensitivities* have been identified for certain sarcoma subtypes.

**Trials 2000-present**
- Subgroup of sarcomas with a certain karyotype presenting with somatic genomic amplifications, mutations or translocations:
  - results in a fusion gene or protein that is potentially targetable
  - accounts for 20% of STS

*Era of histology-driven chemotherapy*

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**Histology-driven Chemotherapy**

**Metastatic, unresectable setting:**

- **Cytotoxic chemotherapy:**
  - Doxorubicin +/- ifosfamide: first-line therapy
    - if goal is disease stabilization or limit toxicities, single agent doxorubicin should be considered
    - if goal is to maximize tumor response, then multiagent therapy should be considered

- **Trabectedin**
  - approved in Europe
  - efficacy against myxoid/round cell liposarcoma and leiomyosarcomas
  - Phase II trabectedin + doxorubicin for leiomyosarcoma: CR+PR 38%, SD 51% for ST-LMS
  - Phase III trabectedin vs DTIC in pts with LPS or leiomyosarcomas (NCT01343277)

Gronchi, Expert Rev Anticancer Ther. 14(6), 689-704; 2014
**Histology-driven Chemotherapy**

**Metastatic, unresectable setting:** (cytotoxic continued)

- **Gemcitabine + docetaxel**
  - activity in LMS, undifferentiated pleomorphic sarcoma, angiosarcoma
  - Phase III doxorubicin vs gem-docetaxel for advanced STS (NCT01574716)

- **Taxanes**
  - activity in angiosarcoma
  - ORR 40-65%
  - improved efficacy when combined with doxorubicin?

- **Dacarbazine (DTIC)**
  - activity in LMS
  - single agent or in combination with gemcitabine or doxorubicin

- **Etoposide + ifosfomide**
  - activity in MPNST
  - Phase III trial ongoing

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**Histology-driven Chemotherapy**

**Metastatic, unresectable setting:**

- **mTOR inhibitors**
  - *sirolimus*
    - activity in PECOMA, myxoid chordrosarcoma
  - *everolimus*
    - activity in angiosarcoma
    - Phase II 67% PFS at 16 weeks in angiosarcoma subgroup
  - *ridaforolimus*
    - Phase III in pts w mets sarcoma who achieved favorable response to first line conventional chemo received either ridaforolimus vs placebo: 28% RR for progression
Histology-driven Chemotherapy

Metastatic, unresectable setting:

• **Targeted therapy**
  
  • **Imatinib**
    • activity DFSP
    • ORR 50% in Phase II trials
  
  • **Pazopanib**
    • activity in non-lipogenic tumors specifically leiomyosarcoma and synovial sarcoma
    • PALETTE-EORTC 62072 of pazopanib vs placebo as second line in non-lipogenic tumors showed an improvement in OS (12.5 months vs 10.7 months)
    • numerous phase II trials ongoing

Histology-driven Chemotherapy

Metastatic, unresectable setting:

• **Targeted therapy**
  
  • **MDM2/CDK4 inhibitor**
    • activity in WDF-LPS and DDF-LPS
    • ongoing phase III trial for CDK4 vs placebo
  
  • **Sunitinib and Cediranib**
    • activity in alveolar soft part sarcoma and solitary fibrous tumors
    • ORR of 84%
    • Phase II/III cediranib vs sunitinib for ASPS (NCT 01391962)
  
  • **IGF-1R, HDAC, and Hedgehog inhibitors**
    • too early to say...
**Histology-driven Chemotherapy**

**Adjuvant chemotherapy**

- Meta-analysis evaluation
  - evaluated 18 prospective RCTs—1953pts
  - doxorubicin-based chemotherapy
  - absolute benefit in relapse free survival of 10%
  - improvement in overall survival of 5%

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**Summary #2**

- “It remains difficult to quantify the risk of recurrence for an individual patient and it is often physician bias, experience, and gestalt, which ultimately determines therapy”.

- Subtype-specific deviations from a common algorithm are needed.

- The modern concept of *histology-driven* chemotherapy has been accepted and should be employed.

- These patients should be managed in a multidisciplinary setting with clinicians specializing in the treatment of sarcomas.
Questions

Neoadjuvant chemotherapy

- No prospective study has definitively shown a benefit to administration of adjuvant chemotherapy in STS patients.
- Three groups of patients that we should consider neoadjuvant therapy:
  - **Group 1** — high-risk of metastases
    - Rhabdomyosarcoma (median survival 22 months)
    - Ewing sarcoma (5 years DSS 50-60%)
  - **Group 2** — high-grade tumors larger than 10cm
  - **Group 3** — moderate size tumors (5-10cm) that are chemosensitive
    - Round cell LPS
    - Pleomorphic LPS
    - Synovial sarcoma
    - Leiomyosarcoma

Is Surgical Resection Sufficient for the Management of Pure Myxoid Liposarcomas?
A Multi-Institutional Series of Pure Myxoid Liposarcomas of the Extremities and Torso

Katherine J. Baxter, MD, Sarah B. Fisher, MD, Jonathan S. Zager, MD,1, Nicholas Gooyeyey, BS,1, Jukes P. Namm, MD, Thomas Krausz, MD, Sharon W. Weiss, MD,2, David K. Monson, MD,1, Ricardo J. Gonzalez, MD,2,3, David Cheong, MD,3, G. Douglas Letson MD,4, Marilyn M. Bui, MD, PhD,5, Kevin K. Roggin, MD,6, Keith A. Delman, MD,7, Kenneth Cardona, MD

<table>
<thead>
<tr>
<th>Variable</th>
<th>No XRT (n=47)</th>
<th>XRT (n=53)</th>
<th>p-value</th>
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<td>53</td>
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<td>32 (65%)</td>
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<tr>
<td>Race</td>
<td>White</td>
<td>17 (75%)</td>
<td>Other</td>
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<td>Black</td>
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<td>3 (5%)</td>
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<td>2 (13%)</td>
<td>1 (7%)</td>
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<td>ARA</td>
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<td>6 (32%)</td>
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<td>3</td>
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<td>4</td>
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<td>1 (2%)</td>
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<tr>
<td>Smoking</td>
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<td>25 (48%)</td>
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<td>Tumor Location</td>
<td>Thoracic</td>
<td>3 (18%)</td>
<td>9 (34%)</td>
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<td>Upper Extremity</td>
<td>1 (6%)</td>
<td>3 (5%)</td>
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<tr>
<td>Lower Extremity</td>
<td>13 (77%)</td>
<td>46 (79%)</td>
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<td>Preoperative biopsy</td>
<td>10 (65%)</td>
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<td>Length of stay</td>
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<td>2.1</td>
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<td>Any complication</td>
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<td>17 (30%)</td>
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<tr>
<td>Wound complication</td>
<td>2 (13%)</td>
<td>36 (68%)</td>
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<td>Malignancy</td>
<td>0</td>
<td>33 (19%</td>
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<td>Tumor Size (cm)</td>
<td>13</td>
<td>11</td>
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<tr>
<td>Depth</td>
<td>Deep</td>
<td>14 (61%)</td>
<td>57 (108)</td>
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<td>Superficial</td>
<td>3 (18%)</td>
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<td>Positive Margin</td>
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<td>Any Recurrence</td>
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<td>23 (43%)</td>
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<td>Local recurrence</td>
<td>0</td>
<td>2 (13%)</td>
<td>0.7</td>
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Too much: Desmoid tumors (Aggressive Fibromatosis)


Treatment Algorithm