Introduction to Sarcoma

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Objectives

- Appreciate the heterogeneity in sarcoma and its impact on management
- Recognize the red flags of sarcoma and importance of sub-specialty management
- Highlight key post-care challenges patients who undergo curative treatment for sarcoma face
Sarcomas

- 1,762,450 new cases of cancer expected in 2019
  - 606,880 cancer deaths
- 16,250 cases of bone and soft tissue sarcoma (~1%)
  - 6,930 deaths from sarcoma predicted
- Median age at diagnosis: 6th decade
  - Varies based on type of sarcoma
- Soft tissue sarcoma distribution:
  - Thigh/buttock/groin – 46%
  - Torso – 18%
  - Upper extremity – 13%
  - Retroperitoneum – 13%
  - Head and neck – 9%

American Cancer Society, 2019
Sarcomas

• Comprise a group of neoplasms of mesenchymal origin

• Heterogeneous, >70 subtypes

• Requires experienced bone and soft tissue pathologist
  • ~40% cases read by general pathologist modified by expert BST pathologist

Sarcomas

Bone ~20%

Chemosensitive
Osteosarcoma
Ewing Sarcoma

Chemoresistant
Chondrosarcoma

Soft Tissue ~80%

Non-GIST

Aggressive - Chemosensitive
UPS
Leiomyosarcoma
Myxoid round cell liposarcoma
Synovial sarcoma

GIST

Indolent - Chemoresistant
Well diff LPS
Alveolar soft part sarcoma
Malignant solitary fibrous tumor
Sarcomas

• Patients with **localized sarcomas** can be treated with curative intent
  • ~62% long-term survival
  • Adverse risk factors
    • Size > 5cm
    • Deep tumors
    • Higher grade

• Patients with **disseminated disease** treated with palliative intent
  • Goal: improve quality and duration of life
  • Median survival ~1-2 years
Sarcomas

• Strategies to improve patient outcomes:
  • **Earlier diagnosis**
  • More effective therapies:
    • Subtype specific
    • Biomarker driven
Question 1

• On average, how many soft tissue lumps seen in the primary care practitioner’s clinic end up being malignant?
  • A. 30 in 100
  • B. 1 in 100
  • C. 5 in 100
  • D. 10 in 100
Question 2

• Pain is a great discriminator in discerning malignant potential of a soft tissue lump
  • A. True
  • B. False
New Soft Tissue Lumps

- Estimated 1 in 100 new cases of soft tissue lumps seen by PCP is **malignant**

- **Inexperienced** results in:
  - Delay in diagnosis
  - Inadvertent excisions

Nandra et al. EJSO. 2015
Brouns et a. EJSO. 2003
Delays in Diagnosis and Referral

• Delayed diagnosis results in:
  • Larger tumor size at presentation
  • Poorer resection margin
  • Lower likelihood of limb salvage
  • Increased rate of post-surgical complications
  • Increased likelihood of metastatic disease
  • Worse overall survival

Nandra et al. EJSO. 2015
Brouns et al. EJSO. 2003
Delays in Diagnosis and Referral

- Etiology of delayed diagnosis:
  - Patient related delays
    - Absence of pain in lump
  - Physician related delays
    - Misdiagnosis
    - Clinical exam only in 59%

Brouns et al. EJSO. 2003
Clark and Thomas. EJSO. 2005
Case 1

46 y F

18 month history of slowly progressive painless “lump” in left thigh

Finally complained to PCP at last GME
  - CT extremity
    - >30 cm length lobulated mass

Bx + myxoid liposarcoma
Case 2

- 44 y F with 3 year history of pain
- 8 mo. change in pain and growing lump
- PCP orders X-ray then CT of the knee
  - >3 cm mass
- Referred to surgeon
  - Excisional biopsy and arthroscopy
  - Margin + synovial sarcoma
Inadvertent Excisions

- Estimated to account for 40% of initial sarcoma surgeries

- Why does this matter?
  - Residual disease
  - Reports ranging from 24-74%
  - Higher rate of local relapse (70-90%)
  - Decreased disease specific survival

Venkatesan et al. EJSO. 2012
Inadvertent Excisions

• Role of **definitive wide re-excision**
  • Adequate local control can be achieved
  • Disease specific survival similar to those who undergo primary excision of known sarcoma

Arai et al. Clin Orthop Relat Res. 2010
Inadvertent Excisions

• **Downstream impact** of wide re-excision
  • Increases likelihood of free flap for limb salvage procedures
  • Greater likelihood of neoadjuvant/adjuvant radiation
  • *Doubles the financial burden*

Thacker et al. Foot and Ankle International. 2008
Inadvertent Excisions

- Review of University Health System Consortium and Association of American Medical Colleges database
  - 2007-2009
    - 50% of deep and malignant soft tissue tumor resections performed by non-oncologic surgeons
    - 17% performed by practitioners who did 1-2 per year

RED FLAGS

• Size > 5cm
• Increasing size
• Deep location
• Painful
• Recurrent mass after previous excision

Best Predictors?

- Royal Orthopedic Hospital, UK
  - 3018 patients with soft tissue lump, 1996-2007
    - Malignant vs Benign
      - Increase in size
      - Age of the patient
      - Size of the lump
      - Duration of symptoms
      - Pain was a poor discriminator
    - Greatest pairing was *growing golf ball sized lesion*

Nandra et al. EJSO. 2015
Question 4

• The standard of care for the management of localized high risk soft tissue sarcomas includes:
  • A. Surgery only
  • B. Surgery with or without radiation
  • C. Surgery in combination with chemotherapy and radiation
  • D. All of the above
Case 4

• 70 y M

• Notices painless lump while in the shower

• MRI shows 9.6 cm proximal thigh mass

• Biopsy + high grade myxofibrosarcoma

• Staging studies show no evidence of metastases
Case 4

- Preoperative radiation with radiosensitizing chemotherapy
- Resection of necrotic and cystic mass with 90% necrosis
- Adjuvant chemotherapy with doxorubicin and ifosfamide
- 5 year f/u no evidence of disease
Radiation in Localized STS

- Improves local control
- No impact on overall survival

Yang et al J Clin Onc 1998
Chemotherapy in Localized STS?

- **Overall survival benefit:**
  - Controversial
    - SMAC 1997
      - negative
    - SMAC 2008
      - ARR death of 11%
      - Doxorubicin and Ifosfamide
    - EORTC 62931
      - No benefit
      - 24% patients had small tumors & lower grade

- **Aid operability shrinking locally advanced**
  - Heterogeneous
  - Impact of subtype on treatment choice
  - Some are refractory to conventional cytotoxic therapy
    - *Rarely* see shrinkage with targeted agents unless driver mutation

SMAC. Lancet. 1997
Pervaiz. Cancer 2008
Woll et al Lancet Oncology 2012
## Response to Systemic Therapy

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Response Rate</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Doxorubicin/Ifosfamide</td>
<td>30-40%</td>
<td>Improved RR compared to doxorubicin; no survival advantage</td>
</tr>
<tr>
<td>High-dose ifosfamide</td>
<td>15-20%</td>
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<tr>
<td>Gemcitabine/Docetaxel</td>
<td>15-30%</td>
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<tr>
<td>Doxorubicin</td>
<td>10-15%</td>
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<tr>
<td>Trabectedin</td>
<td>5-10%</td>
<td>Liposarcoma/Leiomyosarcoma Only</td>
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<tr>
<td>Eribulin</td>
<td>5-10%</td>
<td>Liposarcoma Only</td>
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<tr>
<td>Dacarbazine</td>
<td>5-10%</td>
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<tr>
<td>Pazopanib</td>
<td>5%</td>
<td>All subtypes except Liposarcoma</td>
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### Adjuvant Systemic Therapy in GIST?

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>Arms (Imatinib)</th>
<th>RFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>ACOSOG Z9001</td>
<td>1 yr. vs 0</td>
<td>Improved</td>
<td>No Difference</td>
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<tr>
<td>EORTC 62024</td>
<td>2 yrs. vs 0</td>
<td>Improved</td>
<td>No Difference</td>
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<tr>
<td>SSG XVIII/AIO</td>
<td>3 yrs. vs 1 yr.</td>
<td>Improved</td>
<td>Improved</td>
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</table>

Adjuvant Systemic Therapy in GIST?

- DeMatteo et al. Lancet. 2009
- Casali et al. JCO. 2015
- Joensuu et al. JAMA. 2012
Chemotherapy in Localized Ewing sarcoma

Chemotherapy in Localized Osteosarcoma

- Pivotal trial by Link et al
  - 2 yr RFS of 66% (chemotherapy) vs 17% (observation)

EURAMOS1: 76% 3-yr-EFS

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<td>Cycle</td>
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<th>SURGERY</th>
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Fig 1. Methotrexate, doxorubicin, cisplatin chemotherapy regimen. A, doxorubicin 37.5 mg/m²/d, days 1 and 2; P, cisplatin 60 mg/m²/d, days 1 and 2; M, methotrexate 12 g/m²/d.

Link et al. NEJM. 1986
Impact of Treatment.....
Survivors of extremity sarcoma treatment

• As compared to healthy controls:
  • **Decreased physical functioning**
    • Pain, reduced joint mobility, increase fall risk (amputees and poor prostheses), lymphedema (large/deep tumors)
  • **Psychologic morbidity**
    • Reports vary from 15-70%
  • **Negative social impact**
    • Less likely to marry, live independently, be employed, attend college

Kee Kwong. EJSO. 2014
Gerrand and Furtado. Clin Oncol. 2017
### Anxiety and Depression

Prospective Study of 146 sarcoma patients in 3 Portuguese cancer units

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis N (%)</th>
<th>Treatment N (%)</th>
<th>Follow up N (%)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
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<tr>
<td>Normal</td>
<td>15 (36.6%)</td>
<td>17 (47.2%)</td>
<td>34 (55.7%)</td>
<td>.31</td>
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<tr>
<td>Mild</td>
<td>14 (34.1%)</td>
<td>10 (27.8%)</td>
<td>14 (23%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (19.5%)</td>
<td>8 (22.2%)</td>
<td>12 (19.7%)</td>
<td></td>
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<tr>
<td>Severe</td>
<td>4 (9.8%)</td>
<td>1 (2.8%)</td>
<td>1 (1.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>26 (61.9%)</td>
<td>20 (55.6%)</td>
<td>47 (77%)</td>
<td>.32</td>
</tr>
<tr>
<td>Mild</td>
<td>8 (19%)</td>
<td>9 (25%)</td>
<td>10 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (11.9%)</td>
<td>4 (11.1%)</td>
<td>3 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3 (7.1%)</td>
<td>3 (8.3%)</td>
<td>1 (1.6%)</td>
<td></td>
</tr>
</tbody>
</table>

**Key Findings:** Majority of patients have mild anxiety and depression. Symptomatic patients: Recurrence (diagnostic phase), Female (Treatment phase), Older patients and shorter time from d/c treatment (Follow up phase)

### Oncofertility

<table>
<thead>
<tr>
<th>Eligible Patients</th>
<th>% oncologists who agree should be done</th>
<th>% oncologists who perform at least 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility preservation counseling</td>
<td>86%</td>
<td>47%</td>
</tr>
<tr>
<td>Sperm banking</td>
<td>92%</td>
<td>72%</td>
</tr>
<tr>
<td>Refer to fertility specialist</td>
<td>73%</td>
<td>30%</td>
</tr>
</tbody>
</table>

- Sarcomas account for 10% cancers in adolescents and young adults
- >40% will have some form of reproductive dysfunction (radiation to pelvis or systemic therapy)
- Animal models of newer sarcoma agents have less infertility risk compared with conventional chemotherapy (DNA binding, targeted, tyrosine kinase inhibitors)
Conclusions

• Recognition of suspicious lumps and imaging before biopsy can improve outcome

• Minimize referring patients with “sarcoma suspicious lumps” to non-oncologic surgeons

• Early involvement of experienced sarcoma center improves outcome and is strongly encouraged

• Recognition of treatment consequences and prompt implementation of personalized rehabilitation and psychosocial services is needed
reininsarcoma.org
Questions & Discussion

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