Sarcomas in Children

Langerhans Cell Histiocytosis

3rd Intensive Review in Pediatric Hematology/Oncology 2018
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Management of Sarcomas

BONE SARCOMAS
- Ewing Sarcoma
- Osteosarcoma

SOFT TISSUE SARCOMAS
- Rhabdomyosarcoma
- Soft Tissue Sarcomas
Management of Sarcomas

**BONE SARCOMAS**
- Ewing Sarcoma
- Osteosarcoma

**SOFT TISSUE SARCOMAS**
- Rhabdomyosarcoma
- Soft Tissue Sarcomas
Principles of Management

- Age
- Site
- Symptoms (Race)

Clinical assessment → Make your first differential diagnosis → Imaging → Make your second differential diagnosis → Biopsy

Primary Mets (bones, lungs)

Diagnosis and Stage → MD Team → Risk Stratification → Start treatment

Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)
Principles of Management

- **Induction Chemotherapy**
- **Adjuvant Chemotherapy**
  - Same Agents

**RISK STRATIFICATION**

**Type of LOCAL CONTROL**

- **SURGERY**
- **RT**

*Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)*
Management of Sarcomas

BONE SARCOMAS
- Ewing Sarcoma
- Osteosarcoma

SOFT TISSUE SARCOMAS
- Rhabdomyosarcoma
- Soft Tissue Sarcomas
Figure VIII.2: Bone cancer age-specific incidence rates by histology
all races, both sexes, SEER, 1976-84 and 1986-94 combined

Average annual rate per million

- All Bone
- Osteosarcoma
- Ewing's Sarcoma
- Chondrosarcoma

Age (in years) at diagnosis
# Malignant Bone Tumors

<table>
<thead>
<tr>
<th></th>
<th>Osteosarcoma</th>
<th>Ewing’s Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>12-18</td>
<td>5-25</td>
</tr>
<tr>
<td>Adult &gt; 40 yr</td>
<td>Yes</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Asian &gt; Caucasian</td>
<td>Caucasian &gt; Asian</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Ye</td>
<td>No</td>
</tr>
<tr>
<td>Previous RT</td>
<td>Ye</td>
<td>No</td>
</tr>
<tr>
<td>Family Hx</td>
<td>LFS, RB1</td>
<td>No</td>
</tr>
<tr>
<td><strong>Constitutional symptoms</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Bone</td>
<td>Bone, soft tissue, renal</td>
</tr>
<tr>
<td><strong>Skip lesion</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>Lung</td>
<td>Lung, bone, BM</td>
</tr>
</tbody>
</table>
# Malignant Bone Tumors

<table>
<thead>
<tr>
<th></th>
<th>Osteosarcoma</th>
<th>Ewing’s Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone</strong></td>
<td>Long bones</td>
<td>Long and Flat bones (Pelvis, skull, ribs)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Metaphysis</td>
<td>Diaphysis</td>
</tr>
<tr>
<td><strong>Genetic</strong></td>
<td>Rb, p53, TS genes</td>
<td>t(11;22)EWS-FLI Oncogene activation</td>
</tr>
<tr>
<td><strong>Radiologic findings</strong></td>
<td>• Sunburst pattern  &lt;br&gt;• Calcification</td>
<td>• Moth-eaten lytic lesion  &lt;br&gt;• Onion skin  &lt;br&gt;• Periosteal reaction  &lt;br&gt;• Codman’s triangle</td>
</tr>
<tr>
<td><strong>LAB</strong></td>
<td>↑ALP, CBC-normal</td>
<td>Normal ALP, CBC-abnormal (if BM+)</td>
</tr>
<tr>
<td><strong>PATH</strong></td>
<td>Osteoblast</td>
<td>Small round blue cell, primitive neuroectodermal cell</td>
</tr>
<tr>
<td></td>
<td>Malignant osteoid +</td>
<td>No malignant osteoid</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>Resistance</td>
<td>Responsive</td>
</tr>
</tbody>
</table>
## Bone Tumors in Children

<table>
<thead>
<tr>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal Femur</td>
</tr>
</tbody>
</table>
Ewing Sarcoma Family of Tumors (ESFT)

- Majority present in the 2\textsuperscript{nd} decade of life
- 2\textsuperscript{nd} MCM bone malignancy in children
- Bone, soft tissue, Askin’s tumor or PNET
- Metastasis: 25% of patients present with metastases
  - Lung 38%
  - Bone 31%
  - BM 11%
  - Other unusual sites

Mascarenhas et al., 2006
SEER Data 1975-1999

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK
Site of Origin

- **Bone primaries (75%)**
  - Axial = extremities
    - Pelvis
    - Long bones
    - Other axial sites
- **Soft tissue primaries (25%)**
  - Paraspinal
  - Chest wall
  - Various other sites

Mascarenhas et al., 2006
SEER Data 1975-1999
## Primary Sites of ESFT of Bone

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Axis</strong></td>
<td>52-55%</td>
</tr>
<tr>
<td>Skull</td>
<td>2-6%</td>
</tr>
<tr>
<td>Clavicle/Scapula</td>
<td>4-6%</td>
</tr>
<tr>
<td>Ribs</td>
<td>12-13%</td>
</tr>
<tr>
<td>Spine</td>
<td>6-8%</td>
</tr>
<tr>
<td>Pelvis</td>
<td>23-27%</td>
</tr>
<tr>
<td><strong>Extremities</strong></td>
<td>41-47%</td>
</tr>
<tr>
<td>Humerus</td>
<td>5-7%</td>
</tr>
<tr>
<td>Radius/Ulna</td>
<td>1-3%</td>
</tr>
<tr>
<td>Hand</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Femur</td>
<td>16-19%</td>
</tr>
<tr>
<td>Tibia</td>
<td>7-10%</td>
</tr>
<tr>
<td>Fibula</td>
<td>6-9%</td>
</tr>
<tr>
<td>Foot</td>
<td>2-3%</td>
</tr>
</tbody>
</table>
Regional Node Involvement

• Overall low incidence (6%)
• Higher incidence in soft tissue tumors (12% vs. 3%)
• Higher incidence in axial tumors

![Graph showing overall survival by regional lymph node status]
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Translocation</th>
<th>Fusion Gene</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing sarcoma</td>
<td>t(11;22)(q24;q12)</td>
<td>EWSR1/FLI1</td>
<td>80-95%</td>
</tr>
<tr>
<td></td>
<td>t(21;22)(q22;q12)</td>
<td>EWSR1/ERG</td>
<td>5-10%</td>
</tr>
<tr>
<td></td>
<td>t(7;22)(p22;q12)</td>
<td>EWSR1/ETV1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(17;22)(q12;q12)</td>
<td>EWSR1/ETV4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q35;q12)</td>
<td>EWSR1/FEV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(16;21)(p11;q22)</td>
<td>TLS/ERG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;16)(q35;p11)</td>
<td>TLS/FEV</td>
<td></td>
</tr>
<tr>
<td>Ewing-like sarcoma</td>
<td>t(20;22)(q13;q12)</td>
<td>EWSR1/NFATC2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(NB: can occur in ring chromosome and may be amplified)</td>
<td>EWSR1/POU5F1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(6;22)(p21;q12)</td>
<td>EWSR1/SMARCA5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(4;22)(q31;q12)</td>
<td>EWSR1/ZSG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Submicroscopic inv(22) in t(1;22) (p36.1;q12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q31;q12)</td>
<td>EWSR1/SP3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(4;19)(q35;q13)</td>
<td>CIC/DUX4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inv(X) (p11.4;p11.22)</td>
<td>BCOR/CCNB3</td>
<td></td>
</tr>
</tbody>
</table>
Investigations

Primary site
- Plain film
- MRI of affected region

Metastasis detection and staging
- CT chest
- Bone scan
- Bilateral BM biopsy
- PET scan

Tissue biopsy
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK
Diagnosis-Pathology

- Small round blue cell tumor
- Neural differentiation with PNET
- Nearly universal membranous CD99 expression
- Molecular diagnostics
  - Cytogenetics
  - FISH
  - PCR
Principles of Management

Induction Chemotherapy → LOCAL CONTROL → Adjuvant Chemotherapy

RISK STRATIFICATION
Euro-EWING approach vs. COG approach

Type of LOCAL CONTROL

Surgery

RT

Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)
## Local Control

<table>
<thead>
<tr>
<th>Approach</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete surgical resection</td>
<td>Not an option for all tumors</td>
</tr>
<tr>
<td>Radiation</td>
<td>Late effects of therapy</td>
</tr>
</tbody>
</table>
| Surgery plus radiation          | • Late effects of therapy  
• Prolonged local control interferes with systemic therapy                   |

- Patients treated with definitive radiation have higher risk of local failure
- Overall survival not different based upon mode of local control
- Favor surgical resection whenever feasible, with radiation reserved for selected cases
Prognostic factors

- Age at presentation: ≥ 14 yrs
- Site of disease: pelvic
- Size of tumor: > 200 ml or > 8 cm
- CMT without IE
- Stage
  - Localized: 5 year EFS ~ 70%
  - Metastatic: 5 year EFS < 30%
    - Isolated lung metastases do slightly better
    - High dose chemotherapy: modest benefit with significant toxicity

Cotterill et al., 2000
Rodriguez-Galindo C, Cancer 2007
Marina et al., Sarcoma 2015
AEWS-0031 – Chemotherapy Intensification through Interval Compression for Ewing Sarcoma

### Drugs and Cycles

**VDC x 7 cycles***
- (V) Vincristine 2 mg/m² day 1
- (D) Doxorubicin 75 mg/m² CI for 48 hours
- (C) Cyclophosphamide 1200 mg/m² day 1 (+Mesna)
  - G-CSF 5 mcg/kg/d until ANC > 750/mm³

**IE x 7 cycles**
- (I) Ifosfamide 1800 mg/m²/day days 1 - 5 (+ Mesna)
- (E) Etoposide 100 mg/m²/day days 1 – 5
  - G-CSF 5 mcg/kg/d until ANC > 750/mm³

### Diagnosis

- **Induction**
  - **Standard**
    - 4 cycles/12 weeks
  - **Compressed**
    - 6 cycles/12 weeks

### Randomize

- **Primary tumor treatment**

- **Continuation**
  - **Standard**
    - 10 cycles/30 weeks
  - **Compressed**
    - 8 cycles/16 weeks
AEWS-0031 – Chemotherapy Intensification through Interval Compression for Ewing Sarcoma

5-yr EFS 73%

5-yr EFS 65%

5-yr OS 83%

5-yr OS 77%

P=0.048
Management of Sarcomas

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- Soft Tissue Sarcomas
Incidence of Soft Tissue Sarcomas According to Age

Malignant Fibrous Histiocytoma

Malignant Peripheral Nerve Sheath Tumors

Liposarcoma

Fibrosarcoma

Synovial sarcoma

Rhabdomyosarcoma

Age 0 10 20 30 40 50 60 70 yrs

A. Ferrari, MD
RMS vs NRSTS

**RMS**
- Age < 10
- H&N
- Unresected (50%)
- Two histologic types
- Chemosensitive
- Adjuvant therapy is effective
- Metastases: lung, bone, bone marrow
- Rx: Risk based-VAC

**NRSTS**
- Age > 10
- Extremities
- Resected (70%)
- Many histologic types
- Chemoresistant
- Unproven benefit of adjuvant therapy
- Metastases: lung; other sites are rare
- Rx: Ifos/Dox
Management of Sarcomas

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SOFT TISSUE SARCOMAS
- Rhabdomyosarcoma
- Soft Tissue Sarcomas
## Disease characteristics

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Frequency (%)</th>
<th>Symptoms and signs</th>
<th>Predominant pathologic subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>35</td>
<td></td>
<td>Embryonal</td>
</tr>
<tr>
<td>Orbit</td>
<td>9</td>
<td>Proptosis</td>
<td></td>
</tr>
<tr>
<td>Parameningeal</td>
<td>16</td>
<td>Cranial nerve palsies; aural or sinus obstruction +/- drainage</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>Painless, progressively enlarging mass</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>22</td>
<td></td>
<td>Embryonal (botryoid variant in bladder and vagina)</td>
</tr>
<tr>
<td>Bladder and prostate</td>
<td>13</td>
<td>Hematuria, urinary obstruction</td>
<td></td>
</tr>
<tr>
<td>Vagina and uterus</td>
<td>2</td>
<td>Pelvic mass, grape liked mass, vaginal discharge</td>
<td></td>
</tr>
<tr>
<td>Paratesticular</td>
<td>7</td>
<td>Painless mass</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>18</td>
<td>Affects adolescents; swelling of affected body part</td>
<td>Alveolar (50%)</td>
</tr>
<tr>
<td>Perineal and perianal (PRMS)</td>
<td>2</td>
<td>Mass</td>
<td>Alveolar (60-80%)</td>
</tr>
<tr>
<td>Other</td>
<td>23</td>
<td>Mass</td>
<td>Embryonal, alveolar</td>
</tr>
</tbody>
</table>
Rhabdomyosarcoma

HISTOLOGY

- Embryonal 55-60%
- Botryoid 6%
- Alveolar 15-20%
- Undiff 20%
Prognostic Factors

• TNM
  – Diameter \( \leq 5 \text{cm} \) with improved survival  
    (correlation between size and BSA*)
  – Metastasis and regional LN involvement
• Resectability
• Age: 1-9 yo have best prognosis
• Sites of primary tumor
• Histopathology

* Ferrari et al., JCO, 2009
Prognostic Factors: Sites of primary tumor

- **Favorable**
  - Orbit
  - GU non bladder, non prostate
  - H&N non parameningeal
  - Biliary tract

- **Unfavorable**
  - Bladder
  - Prostate
  - Parameningeal
  - Extremities
  - (Perineal and perianal)*

*Casey et al., Int J Radiation Oncol Biol, 2014
Fuchs et al., Annals of Surgery, 2014
Prognostic Factors:

Histopathology

Favorable

• Embryonal
• Botryoid (under mucosa of the vagina, bladder, nasopharynx and biliary tract)
• Spindle cell (mostly at paratesticular site)

Unfavorable

• Alveolar
• Anaplastic* (not influence treatment)
Prognostic Factors
Histologic Subtypes of RMS
Failure-free Survival, IRS-IV Patients

Embryonal
Alveolar

Years
Fail-time Survival

Embryonal
Alveolar

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK
Molecular Biologic Characteristics

- Alveolar: 70-80% fusion gene positive FOXO1
  - PAX3/FOXO1, PAX7/FOXO1
  - Outcome ARMSn = ERMS

Nathan and Oski’s Hematology and Oncology of Infancy and Childhood 7th ed, 2009

Williamson et al., JCO, 2010
Investigations

• CT/ MRI primary lesion
• CT chest, CXR
• CT abdomen include pelvis
• Bone scan
• PET scan
• BMA & BM biopsy
• Biopsy
  – ARMS with extremities lesions → sentinel LN Bx
Risk Stratification

- Staging
  - Pre-surgical Sites and TNM
- Grouping
  - Post-surgical Resectability
- Histology
- Risk
IRSG staging system 1972

<table>
<thead>
<tr>
<th>Stage</th>
<th>Site</th>
<th>Tumor size (T)</th>
<th>LN (N)</th>
<th>Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Favorable</td>
<td>Any</td>
<td>Any</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Unfavorable</td>
<td>≤ 5 cm</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Unfavorable</td>
<td>≤ 5 cm</td>
<td>Positive</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Favorable: Orbit, GU non bladder, non prostate, H&N non parameningeal, Biliary tract

PM: Middle ear, nasal cavity and paranasal sinuses, nasopharynx and infratemporal fossa/pterygopalatine and parapharyngeal area
LN staging

- Clinical/radiological staging By PE, imaging
- Surgical staging LN resection/biopsy

How’s important??

- LN + CMT + RT
- Clinical/CT Surgical LN Bx +
- no RT −
LN staging

• Extremity site -> sentinel LN biopsy

• Indication for LN Bx
  1. Clinical/radiologional warranted
  2. Extremity site -> sentinel LN biopsy
  3. Boy ≥ 10 yo w paratesticular RMS
LN staging

• Ipsilateral Retroperitoneal LN dissection (RPLND)

Indications

– ≥ 10 yo with paratesticular tumor and abd/pelvis imaging negative
– < 10y w LN positive in CT

➢ Result will distinguish the treatment (esp. RT)

Dang et al., Cancer 2013; 119: 3228-33
COG AOST 0531
IRSG clinical group

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence (%)</th>
<th>Extent of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>Localized disease, <em>completely</em> resected, no residual tumor, no LN</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>Total gross resection with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A. microscopic residual disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B. LN positive, <em>without</em> microscopic residual disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. LN positive, <em>with</em> evidence of microscopic residual disease</td>
</tr>
<tr>
<td>III</td>
<td>49</td>
<td>• Biopsy only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <em>Incomplete</em> resection with gross residual disease</td>
</tr>
<tr>
<td>IV</td>
<td>18</td>
<td>Distant metastatic disease</td>
</tr>
</tbody>
</table>
Risk group assignment algorithm

1. Metastases
   - No
   - Yes

2. Histology
   - Emb
   - Alv

3. Group
   - I or II
   - III

4. Site
   - Fav
   - Unfav

Risk categories:
- Low risk: 35%
- Intermediate risk: 50%
- High risk: 15%
## COG Risk Group

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Incidence (%)</th>
<th>Histology</th>
<th>Pre-Treatment Staging</th>
<th>Post Treatment Clinical Group</th>
<th>5 years FFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-subset A</td>
<td>35</td>
<td>Embryonal</td>
<td>1</td>
<td>I, II, III (orbit)</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>I, II</td>
<td></td>
</tr>
<tr>
<td>Low-subset B</td>
<td></td>
<td>Embryonal</td>
<td>1</td>
<td>III (non-orbit)</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>I, II</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>50</td>
<td>Alveolar</td>
<td>1-3</td>
<td>I, II, III</td>
<td>65-73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embryonal</td>
<td>2,3</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>Any</td>
<td>4</td>
<td>IV</td>
<td>&lt;30%</td>
</tr>
</tbody>
</table>

**LR**: Embryonal Fav

**Unfav** – complete resect

**IR**: Alv Embryonal

**Unfav**- not complete resect

**HR**: Metas
RMS – COG Studies

**LOW-RISK**

Localized ERMS:
- Subset 1:
  - Stage 1, 2 Group I, II
  - Stage 1, Group III (orbit)
- Subset 2:
  - Stage 1, group III
  - Stage 3, Group I, II

**INTERMEDIATE-RISK**

Localized ARMS/UDS:
- Stages 1-3, Group I-III

**HIGH-RISK**

- Stage 4 ARMS/UDS
- Stage 4 ERMS >or< 10 yrs

**ARST0331**

A. VAC x 4 ➔ VA (24 wk)
B. VAC x 4 ➔ VA (48 wk)

**ARST0531**

VAC vs. VAC/VIRN

**D9802**

**ARST0431**

VAC+VIRN+IE

Dose Compression

**D9803**
RMS – COG Studies

**LOW-RISK**

Localized ERMS:
- Subset 1: Stage 1, 2 Group I, II Stage 1, Group III (orbit)
- Subset 2: Stage 1, group III Stage 3, Group I, II

**INTERMEDIATE-RISK**

Localized ARMS/UDS:
- Stages 1-3, Group I-III

Localized ERMS:
- Stages 2-3, Group III

**HIGH-RISK**

Stage 4 ARMS/UDS
- Stage 4 ERMS > or < 10 yrs

**ARST0331**
A. VAC x 4 → VA (24 wk) 89% 98% VAC vs. VAC/VIRN
B. VAC x 4 → VA (48 wk) 66% 86%

**ARST0531**
D9803

**ARST0431**
VAC vs. VAC/VIRN
Dose Compression

FFS OS
- 89% 98% VAC vs. VAC/VIRN
- 66% 86%
• Lessons learned:
  – Results for subset 1 (A) were at least as good as predicted with low dose cyclophosphamide +/- reduced dose XRT
  – FFS for subset 2 (B) is lower than expected with lower dose cyclophosphamide
    • Particularly for Female GU patients who did not receive XRT

Low risk-Subset 2 (B)- recommend VAC
RMS – COG Studies

LOW-RISK

Localized ERMS:
Subset 1:
Stage 1, 2  Group I, II  Stage 1, Group III (orbit)
Subset 2:
Stage 1, group III  Stage 3, Group I, II

INTERMEDIATE-RISK

Localized ARMS/UDS:
Stages 1-3, Group I-III

Localized ERMS:
Stages 2-3, Group III

D9803

HIGH-RISK

Stage 4 ARMS/UDS
Stage 4 ERMS >or< 10 yrs

ARST0431
VAC+VIRN+IE
Dose Compression

ARST0531
VAC vs. VAC/VIRN

ARST0331
A. VAC x 4  →  VA (24 wk)
B. VAC x 4  →  VA (48 wk)

D9802

D9803
IR RMS ARST0531: Overall Survival

Event-free survival ARST0531 by Treatment

VAC: 62% (95% confidence interval: 55%, 69%)
VAV/VI: 62% (95% confidence interval: 55%, 68%) (p=0.85)

Registration: treatment
VAC Only
VAC alternating with VI

CENSOR FAIL TOTAL MEDIAN
147 79 226
150 83 233

Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)
IR RMS ARST0531:

- Lessons learned:
  - Patients treated with VI had no improvement in EFS compared to VAC
  - Nevertheless, VAC/VI treatment resulted in less hospitalization, less use of growth factor, and somewhat similar adverse event experience
  - No evidence to suggest that lower RT dose negatively impacted outcomes

\[ VAC/VI = \text{NEW STANDARD FOR IR RMS IN COG} \]
RMS – COG Studies

**LOW-RISK**

Localized ERMS:
- Subset 1:
  - Stage 1, 2 Group I, II Stage 1, Group III (orbit)
- Subset 2:
  - Stage 1, group III Stage 3, Group I, II

**INTERMEDIATE-RISK**

Localized ARMS/UDS:
- Stages 1-3, Group I-III

Localized ERMS:
- Stages 2-3, Group III

**HIGH-RISK**

Stage 4 ARMS/UDS

Stage 4 ERMS >or< 10 yrs

ARST0431
VAC+VIRN+IE
Dose Compression

ARST0331
A. VAC x 4 → VA (24 wk)
B. VAC x 4 → VA (48 wk)

ARST0531
VAC vs. VAC/VIRN

D9803
Outcome for all patients in ARST0431

**Outcome**
- Failure-free survival
- Overall survival

**Censor**
- 45
- 61

**Fail**
- 64
- 48

**Total**
- 109
- 109

**Median**
- 2.11
- 4.57

**Time (years)**
- 0 to 5.0

**Proportion**
- 0.0 to 1.0
EFS of metastatic RMS

Oberlin RF

- Age ≤ 10 or ≥1 yo
- Unfavorable sites
- Bone or BM involvement
- ≥3 metastatic sites

Oberlin et al., JCO, 2008
EFS of metastatic RMS

Oberlin RF
- Age ≤ 10 or ≥1 yo
- Unfavorable sites
- Bone or BM involvement
- ≥3 metastatic sites

≥2 RF worse prognosis

Brenda J. Weigel et al. JCO 2016;34:117-122
## Risk Tailored Treatment

<table>
<thead>
<tr>
<th>Risk group</th>
<th>CMT (COG)</th>
<th>CMT (TPOG)</th>
<th>RT</th>
<th>EFS</th>
<th>OS</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-subset A</td>
<td>ARST0331 (regimen A)</td>
<td>LR</td>
<td>Group I no RT Wk 1-6</td>
<td>89%</td>
<td>98%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>VAC/Vx24wk</td>
<td>VAC/Vx24wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-subset B</td>
<td>ARST0531</td>
<td>SR</td>
<td></td>
<td></td>
<td></td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>VAC x 42 wk</td>
<td>VAC x42wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>ARST0531</td>
<td>SR</td>
<td>Wk 4</td>
<td>55%</td>
<td>68%</td>
<td>65-73%</td>
</tr>
<tr>
<td></td>
<td>VAC/VI x42 wk</td>
<td>VAC x42wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>ARST0431</td>
<td>HR</td>
<td>Wk 20</td>
<td>38%</td>
<td>56%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td></td>
<td>VDC/IE alt</td>
<td>IVA/CbEV/IVE/VAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VDC/IE/VI x54 wk</td>
<td>x52 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Local Control in RMS

• Depends on size, nodal involvement, and site
  – Orbit, vagina, paratesticular $\rightarrow > 80\%$
  – Trunk, extremities, $> 10$ cm $\rightarrow 60\text{-}70\%$

• Chemotherapy may help with local control
Local Control in RMS Surgery

- Complete resection is preferable, but avoiding radical resections that would impact function
- Primary resection $\rightarrow$ wide excision $\rightarrow$ pseudocapsule
- Muscular tumors $\rightarrow$ complete compartmental resection is not necessary (margin $> 0.5$ cm)
Local Control in RMS
Radiotherapy

• XRT is an effective method to achieve local control for patients with microscopic/gross residual disease

• Dose:
  – 41.4 to 45 Gy for microscopic disease
  – 50.4 to 54 Gy for gross residual disease
Management of Sarcomas

BONE SARCOMAS

- Ewing Sarcoma
- Osteosarcoma

SOFT TISSUE SARCOMAS

- Rhabdomyosarcoma
- Soft Tissue Sarcomas
Incidence of Soft Tissue Sarcomas According to Age

- Malignant Fibrous Histiocytoma
- Malignant Peripheral Nerve Sheath Tumors
- Liposarcoma
- Fibrosarcoma
- Synovial sarcoma
- Rhabdomyosarcoma

Age:

A. Ferrari, MD
Pediatric NRSTS Histologic Subtypes

- Synovial Sarcoma: 35%
- Malignant Peripheral Nerve Sheath Tumor: 24%
- Malignant Fibrous Histiocytoma: 15%
- Fibrosarcoma/Infantile Fibrosarcoma: 11%
- Alveolar Soft Part Sarcoma: 8%
- Other: 7%
Tumor Features

- **Site** (497 w/ pretreatment scans)
  - Extremity 262 (53%)
  - Visceral 106 (21%)
  - Body wall 65 (13%)
  - Head/neck 55 (11%)
  - Unknown 9 (2%)

- **Grade** (551 eligible/evaluable)
  - POG 1 (59; 11%)
  - POG 2 (93; 17%)
  - POG 3 (396; 72%)
  - Indeterminate (3; <1%)

- **Size** (431 eligible/evaluable)
  - ≤ 5 cm (102; 24%)
  - > 5 cm and ≤ 10 cm (166; 38%)
  - >10 cm (163; 38%)

- **Metastases** (14%)
  - Lung (57)
  - Regional nodes (17)
  - Bone (5)
  - Liver (6)
  - Distant nodes (3)
  - Peritoneum (3)
  - Pleura (3)
  - Brain (2)
  - Pancreas (1)
  - Mesentery (1)
  - Leptomeninges (1)
  - Omentum (1)
<table>
<thead>
<tr>
<th>Prognostic Factors in Resected STS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Recurrence</strong></td>
</tr>
<tr>
<td><strong>Distant Recurrence</strong></td>
</tr>
<tr>
<td>EFS</td>
</tr>
<tr>
<td>OS</td>
</tr>
</tbody>
</table>

Diagnosis of eligible soft tissue sarcoma

Non-metastatic

Grossly Resected

Tumor Grade

Low

High

Metastatic to lymph nodes and/or distant sites

Unresected (Unresectable or high grade tumor > 5cm where delayed resection planned)

Maximal Tumor Diameter

≤5cm

>5cm

All Disease Resected?

Yes

No

Microscopic margins ⊗ or ⊕

Microscopic margins ⊗

Microscopic margins ⊕

Arm A Observation

Arm B Adjuvant radiotherapy

Arm C Adjuvant chemo + RT

Arm D Neoadjuvant chemoradiotherapy

Microscopic margins ⊗ or ⊕

Assess Resection Status of Primary Tumor

Grossly resected

Unresected

Arm A Observation

Arm C Adjuvant chemo + RT

Arm D Neoadjuvant chemoradiotherapy

Low Risk

Intermediate Risk

High Risk
Definition of Negative Surgical Margin

*or if tumor excised in continuity with periosteum/fascia

≥ 5mm
ARST 0332 Treatment regimens

Arm B = post-op RT only

- Surgery
- RT 55.8 Gy / 31 Fx
- Week 1

Arm C = post-op RT/chemo

- Surgery
- RT 55.8 Gy / 31 Fx
- Dox/Ifos
- Week 1
- Dox/Ifos
- Ifos
- 4
- 7
- 10
- 13
- 16
- 19
- Surgery/RT to metastatic site

Arm D = neoadjuvant RT/chemo

- Dox/Ifos
- RT 45 Gy / 25 Fx
- Week 1
- Dox/Ifos
- Ifos
- 4
- 7
- 10
- 13
- 16
- 19
- Dox
- Surgery
- Boost Margin + 10.8 Gy Gross 19.8 Gy
- Surgery/RT to metastatic site

IDO 3 g/m² x 3
DOX 75 mg/m² Cl 48 h
Survival by Risk Group

- Low (n=97)
- High (n=27)
- Intermediate (n=51)

- Low grade or high grade ≤ 5 cm, resectable
- High grade > 5 cm or unresectable, regardless of grade

p < .001

Event-Free and Overall Survival

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th># of Patients</th>
<th>4-year EFS (95% CI)</th>
<th>4-year OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (observation)</td>
<td>200</td>
<td>91% (85%, 94%)</td>
<td>97% (89%, 99%)</td>
</tr>
<tr>
<td>B (adjuvant RT)</td>
<td>11</td>
<td>73% (37%, 90%)</td>
<td>100%</td>
</tr>
<tr>
<td>C (adjuvant chemoRT)</td>
<td>109</td>
<td>64% (52%, 74%)</td>
<td>80% (68%, 88%)</td>
</tr>
<tr>
<td>D (neoadjuvant chemoRT)</td>
<td>184</td>
<td>49% (40%, 55%)</td>
<td>63% (54%, 71%)</td>
</tr>
</tbody>
</table>

Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)
Overall Survival

Proportion

Time

Low Risk
Intermediate Risk
High Risk

p<0.001

Overall Survival

B A
C non-met
D non-met
C met
D met

<table>
<thead>
<tr>
<th>Group</th>
<th>Censor</th>
<th>Fail</th>
<th>Total</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-C</td>
<td>11</td>
<td>7</td>
<td>18</td>
<td>2.38</td>
</tr>
<tr>
<td>High-D</td>
<td>29</td>
<td>32</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Int1-C</td>
<td>82</td>
<td>9</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Int2-D</td>
<td>103</td>
<td>20</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Low-A</td>
<td>197</td>
<td>3</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Low-B</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)
Results: 4 yr Cumulative Incidence of Local Failure

Arm B = 9%
Arm C = 13%
Arm D = 14%
p = 0.664
Langerhans Cell Histiocytosis
## Classification of histiocytosis syndrome in children

<table>
<thead>
<tr>
<th>Class</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Langerhans cell histiocytosis (LCH)</td>
</tr>
<tr>
<td></td>
<td>Non-LCH</td>
</tr>
<tr>
<td></td>
<td>- Erdheim-Chester Disease – primary in adult</td>
</tr>
<tr>
<td></td>
<td>- Juvenile xanthogranuloma (JXG) – occur in children and adult</td>
</tr>
<tr>
<td>II</td>
<td>Rosai-Dorfman Disease</td>
</tr>
<tr>
<td></td>
<td>Hemophagocytic lymphohistiocytosis (HLH)</td>
</tr>
<tr>
<td></td>
<td>- Primary HLH – genetic disorder</td>
</tr>
<tr>
<td></td>
<td>- Secondary HLH- infectious associated hemophagocytic syndrome (IAHS)</td>
</tr>
<tr>
<td>III</td>
<td>Malignant histiocytosis (histiocytic sarcoma)</td>
</tr>
<tr>
<td></td>
<td>Monocytic/myelomonocytic leukemias</td>
</tr>
</tbody>
</table>

Adapted from [http://www.cancer.gov/cancertopics/pdq/treatment/lchistio/HealthProfessional](http://www.cancer.gov/cancertopics/pdq/treatment/lchistio/HealthProfessional)
Langerhans Cell Histiocytosis

- Clonal proliferation of “Langerhans Cells”
- Multiple organs and systems can be involved
- Clinical presentation and outcome very variable

Eosinophilic Granuloma
Skin Disease
Polyostotic Bone Disease
Hand-Schuler-Christian
Multi-systemic Disease
Letterer-Siwe
Biology

- Inflammatory response vs. Oncogenic event ???
- Originate from a myeloid-derived precursor
- Uncontrolled clonal periforation of CD1a+/CD207+ cells
- Activation of the MAPK/ERK signaling pathway
  - 60-70% somatic mutation in BRAF (BRAFV600E)
  - 10-25% Others
    - Mutation in MAP2K1
    - Mutation in ARAF
  - ¼ Unknown

Badalian-Very et al., Annu Rev Pathol 2013; 8: 1-20
Badalian-Very et al., Blood 2010; 116: 1919-23
Chakraborty et al., Blood 2014; 124: 3007-15
<table>
<thead>
<tr>
<th>Organ System</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Neuroendocrine deficits, Neurodegeneration</td>
</tr>
<tr>
<td>Skull and craniofacial bones</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>Lung disease (infants, smokers), Thymus</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Liver, Spleen, GI tract</td>
</tr>
<tr>
<td>Skeleton</td>
<td>Bones</td>
</tr>
<tr>
<td>Skin</td>
<td>Cradle cap, seborrhea</td>
</tr>
<tr>
<td>Hematopoietic system</td>
<td>pancytopenia, hypersplenism</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td></td>
</tr>
</tbody>
</table>
# Criteria diagnosis

<table>
<thead>
<tr>
<th>Presumptive diagnosis:</th>
<th>Definitive diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM characteristics compatible</td>
<td>LM plus</td>
</tr>
<tr>
<td>Designated diagnosis</td>
<td>Birbeck granules in the lesional cell by EM and/or</td>
</tr>
<tr>
<td></td>
<td>Positive staining of CD1a antigen and/or CD207 (Langerin) staining on the lesional cell</td>
</tr>
<tr>
<td></td>
<td>≥2 supplemental positive stains for</td>
</tr>
<tr>
<td></td>
<td>• Adenosine triphosphatase</td>
</tr>
<tr>
<td></td>
<td>• S-100 protein</td>
</tr>
<tr>
<td></td>
<td>• α-D-Mannosidase</td>
</tr>
<tr>
<td></td>
<td>• Peanut lectin</td>
</tr>
</tbody>
</table>
Pulmonary involvement in MS LCH

- In multivariate analysis, pulmonary involvement was not an independent prognostic factor.
- Therefore, it was excluded from the definition of risk organ involvement in MS-LCH.

Ronceray et al., J Pediatr 2012; 161: 129-33 e1-3
### Clinical Classification of LCH patients

**LCH-IV**

<table>
<thead>
<tr>
<th>Clinical Classification</th>
<th>Involved System</th>
<th>Involved Organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multisystem LCH (MS-LCH) (Group 1)</td>
<td>≥ 2 RO+/-(e.g. hemato, liver, and/or spleen)</td>
<td></td>
</tr>
</tbody>
</table>
| Single System LCH (SS-LCH) (Group 2) | 1 (UF/MF) | ● Bone UF (single bone) or MF (>1 bone)  
● Skin  
● LN (excluding draining LN of another LCH lesion)  
● **Lungs**  
● Special site (eg. Vertebrae, spine)  
● “CNS-risk”  
● Central nervous system (CNS)  
● Other (e.g. thyroid, thymus) |
Prognosis

- Rapid response to initial treatment within 6 weeks
- Involvement of “Risk organs”; hematopoietic system, liver, spleen and lungs
- Age at diagnosis: diagnosed before 2 years of age, mortality rate 66% (but not include in “Risk”)
- Number of organ involvement: mortality rate is increasing follow by numbers of organ involvement
- Bone involvement associated with favorable prognosis
- Organ dysfunction presented at diagnosis or during the course of disease
- Patients with MFB have excellent prognosis but high tendency for disease reactivation (30-50%) and permanent consequences

Gadner et al., J Pediatr 2001; 138: 728-34
Gadner et al., Blood 2008; 111: 2556-62
Gadner et al., Klin Padiatr 1987; 199: 173-82
Gadner et al., Blood 2013; 121: 5006-14
Treatment
Bone or Skin or LN or Lung

Single system (SS)

Unifocal (UF)
Multifocal (MF)

Or

UF-CNS risk/special site

Multisystem (MS)

RO-
RO+

Liver Spleen Heme
Bone or Skin or LN or Lung

Observation Local Therapy

CMT
Liver → CMT
Spleen → Intensive CMT
Heme
Indications for Systemic Therapy

• SS-LCH with
  – CSN-risk lesions
  – Multifocal bone lesions
  – “Special Site” lesions

• MS-LCH with/without involvement of risk organs
Therapy prolongation improves outcome in RO- MS LCH

- **Survival**

- **Reactivations**

  - 6 mo: 37%
  - 12 mo: 54%

  \[ P = 0.03 \]

Benefit in decreased disease reactivation in prolongation of therapy

*Gadner et al., Blood 2013; 121: 5006-14*
LCH treatment Guideline

GR; good response, PR; partial response, NR; not response, PD; progressive disease
Indication for Treatment

• Low risk LCH (LR)
  – SS-LCH with
    • CSN-risk lesions
    • Multifocal bone lesions
    • “Special Site” lesions
  – MS-LCH without “risk organs”

• High risk LCH (HR)
  – MS-LCH with “risk organs”
LCH treatment Guideline

Induction 1

Induction 2

Continuation 1

Continuation 2

VBL 6 mg/m²

PRD 40 mg/m²/d x 3

PRD 40 mg/m²/d x 5

12 months

24 months

Gadner et al., Blood 2013; 121: 5006-14
LCH-IV Study Protocol
**LCH treatment Guideline**

**Salvage I regimen**

For LR with progressive disease

- **Ara-C 100 mg/m²/d 1-4**
- **VCR 1.5 mg/m² x 1**
- **PRED 40 mg/m²/day**
- **Q 3 wk x 8**
- **6-MP 50 mg/m²/d**
- **MTX 20 mg/m²/wk**

6 months | 18 months

**LCH-IV – Stratum II Second line therapy**

**RO- LCH Reactivation**
LCH treatment Guideline
Salvage II regimen
For HR with progressive disease*

*or NR/PD for Induction-II or NR for Salvage-I protocol

JLSG-96 protocol for LCH patients
Morimoto et al., Cancer 2006; 107: 613-9
Conclusions

• LCH is a neoplastic proliferation of Langerin + myeloid dendritic cells → recruitment of activated lymphocytes

• Wide spectrum of clinical presentations that combine features of neoplastic proliferation with inflammation

• Challenges:
  – Patients with MFB have excellent prognosis but high tendency for disease reactivation (30-50%)
  – Treatment of patients with RO+ disease → Intensive upfront therapy
  – Reactivations → prolongation of therapy
  – Relapse in RO+
HOPE for children with cancer