Ewing’s Sarcoma

RESIDENT LECTURE 6/2014

NIMA NABAVIZADEH
KRISTINA YOUNG
JOSEPH WALLER
Epidemiology

- Neuroectodermal origin
- Adolescents (40%), but 30% in <10 year olds
- 2nd most common bone tumor in children, after osteosarcoma
- ~225 cases/yr
- M:F 1.5-2:1
- white>>black /asian
Ewing Sarcoma Family of Tumors (ESFT)

- ES of bone
- Extra-skeletal ES
- Askin’s tumor
- PNET
So Special They Named It

- **Askin’s tumor**
  - Primary lesion of rib
  - Associated w/ direct pleural extension
  - Significant extraosseous soft tissue mass
  - Female predominance
  - Poor prognosis (median survival: 8 mos)
  - RT delivered to hemithorax, 15-18 Gy
Presentation

- Localized pain and swelling
- Constitutional symptoms 30%
  - fever, low appetite, weight loss
- Distribution
  - Axial skeleton 50%
    - Skull 2%
    - Chest wall 16%
    - Spine 6%
    - Pelvis 26%
  - Extremities
    - Upper 9%
    - Lower 41% (Femur 20%)
- Metastatic disease (20-25%)
  - Primary spread is hematogenous
  - Most commonly to lungs, bones, BM, soft tissue, brain, spine
  - Bilateral bone marrow biopsy part of staging, regardless of tumor size
H/P
Lab: Nonspecific (increased ESR, LDH, WBC)
Imaging studies: x-ray, CT (chest and primary site), MRI, bone scan
PET highly sensitive for detecting bone met (96% sens, 92% spec)
Ongoing study comparing whole body MRI and conventional imaging for detecting distant mets
Biopsy of mass (open preferred) and bone marrow
Imaging Studies

- Bone scan, CXR, CT or MRI of primary, CT of chest
- Plain films show "onion skinning"
  - soft tissue mass growing out from the bone giving rise to multilamellated periosteal reaction vs "sunburst" pattern seen in osteosarcoma.
  - Diaphysis rather than metaphysis (osteosarcoma)
  - Periosteum displaced by underlying tumor
    - Codman triangle
  - New bone formation beyond periosteal margin rare
  - Associated soft tissue mass common
**Primary Tumor:**
- T1 - 8 cm or less in greatest dimension
- T2 - >8 cm
- T3 - discontinuous tumors in the primary bone site

**Regional Lymph Nodes:**
- N0 - no
- N1 – yes

**Distant Metastases:**
- M0 - no
- M1a - lung
- M1b - other distant sites

**Stage Grouping:**
- IA - T1 N0, Low grade
- IB - T2 N0, Low grade; or T3 N0, Low grade
- IIA - T1 N0, High grade
- IIB - T2 N0, High grade
- III - T3 N0, High grade
- IVA - M1a
- IVB - N1, M1b

Note: Ewing's sarcoma is classified as grade 4
<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Size</th>
<th>Node</th>
<th>Metastasis</th>
<th>5y OS</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>Low Grade</td>
<td>&lt; 8cm</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>Low Grade</td>
<td>&gt; 8cm</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>Low Grade</td>
<td>discontinuous (skip) lesion</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>High Grade</td>
<td>&lt; 8cm</td>
<td>none</td>
<td>none</td>
<td>70%</td>
</tr>
<tr>
<td>IIB</td>
<td>High Grade</td>
<td>&gt; 8cm</td>
<td>none</td>
<td>none</td>
<td>70%</td>
</tr>
<tr>
<td>III</td>
<td>High Grade</td>
<td>discontinuous (skip) lesion</td>
<td>none</td>
<td>none</td>
<td>70%</td>
</tr>
<tr>
<td>IVA</td>
<td>Any</td>
<td>Any</td>
<td>none</td>
<td>lung</td>
<td>30%</td>
</tr>
<tr>
<td>IVB</td>
<td>Any</td>
<td>Any</td>
<td>present</td>
<td>other than lung</td>
<td>15%</td>
</tr>
</tbody>
</table>
Small round blue cell tumor
- likely arising in the bone marrow
- Other small round blue cell tumors of childhood include:
  - Neuroblastoma
  - Wilm's Tumor
  - Rhabdomyosarcoma
  - PNET
  - Small cell lymphoma
  - Desmoplastic small round cell tumor

Fusion between EWS gene and a partner gene which dysregulates cell growth
- $t(11;22)$ EWS-FLI1 (85%) \(\rightarrow\) correlates with IHC expression of CD99
- $t(21;22)$ EWS-ERF (10-15%)
**Prognostic Features**

- **Disease site**
  - Favorable: non-pelvic
    - distal, ribs and other having the best prognosis
  - Unfavorable: Pelvic
  - Intermediate: Proximal

- **Age**: younger is favorable

- **Size**: $>8\text{cm}$ is unfavorable

- **Labs**
  - Unfavorable: anemia, elevated ESR, leukocytosis, and elevated LDH

### Table 9.2

- Negative
- Metastases at diagnosis
- Large tumor volume ($>200\text{ mL}$)
- Pelvic/central location of primary
- Age over 17 years
- Positive
- Good response to chemotherapy
Assume occult metastatic disease with chemotherapy as the backbone of treatment
- Radiation alone had cure rate ~10%, with majority failing distally

Chemotherapy is typically given for 12-15 weeks prior to local therapy

Local control is imperative (surgery or radiation therapy or both)
- No randomized studies comparing the two treatment approaches
- Surgery favored if complete resection is feasible without significant morbidity and functional loss
- Radiation favored for central lesions
Surgical Technique

- Limb-salvage preferred, if feasible
- Margins: >1cm bone, >0.5cm STS, >0.2cm fascia
- Preferred for accessible sites
- PORT offered to + margins, gross residual disease
- “Expendable sites”
  - Proximal fibula, lateral 4/5th of clavicle, scapular body, ileum, ischium, pubis, small bones of arms/feet – good functional results with surgery alone with no reconstruction (RT may be avoided in 75% of cases)
Local control: RT

- **Definitive RT**: large tumors, location – vertebra, sacrum, periacetabular pelvis, soft tissue ESFTs
- **Post-op RT**: + margins, poor histological responders, microscopic residual or tumor spill
  - European data (EICSS) – local failure after WIDE RESECTION
    - <1% in good histologic responders (only 10% viable tumor in specimen)
    - 12% for poor responders (>10% viable tumor) → post-op RT brings down to 6%
- **Pre-op RT**: used to downstage large tumors, increasingly used in European protocols
- **Radiation dose**
  - Doses >60 Gy result in unacceptable risk of secondary bone malignancies
  - Doses <40 Gy have unacceptable local failures
  - Currently, ~45 Gy are given for microscopic disease and ~55.8 Gy for gross disease
  - Whole lung radiation used for consolidation after chemotherapy (12-15 Gy)
Local control rates

- Extremity lesions: 90-95% after RT, 70-80% for pelvic tumors
- Tumors > 8cm diameter (80%) vs. 90% in < 8cm
Does VAIA improve outcomes in high-risk (>100ml and/or central-sites) compared to VACA?

n=177, Nonrandomized, Chemo-sandwich

Induction chemo x 3c:
- Standard risk: VACA
- High risk: VAIA

Surgery alone (23%), Surgery + RT (49%), RT alone (28%)
- RT alone: 60 Gy
  - QD vs BID
- Adj RT: 44.8 Gy
  - Proximal/distal margin: 5 cm
  - Deep/lateral margin: 2 cm

Chemo x 9c (12 total)
• 5 yr OS: 69%
• No differences in OS/RFS for local tx
• LC:
  ○ Surgery: 100%
  ○ Surgery + RT: 95%
  ○ RT alone: 86%
    ▪ No difference for QD vs BID
• DM: 24-52%
• Prognostic factors:
  ○ Size (200 mL)
  ○ Response to chemo
  ○ VACA vs VAIA
75pts with pelvic tumors

VACA vs. VACA-IE

Local control modality chosen by physician
- Surgery alone – 16%
- RT alone – 56%
- Surgery +RT – 28%

5yr EFS : 49%

No significant effect of local control modality
Combined results of CESS81, CESS86 and EICESS92 (Schuck, IJROBP, 2003)

- 1058 pts analyzed
- Again, local treatment modality up to physician preference “wherever feasible, a surgical local therapy approach was used”
  - EICESS 92 – pre-op RT introduced for pts with expected close margins
- Local failure significantly lower after surgery (with or without postop RT) than after definitive RT (7.5% vs 26.3%)
- Local control rate with preop RT comparable to that of surgery (7.5% vs 5.3%)
Again, combined results of CESS 86, CESS 81 and EICESS 92

116 pts with primary tumors of C/T/L spine

65% had RT alone, 28% had RT + surgery, 3% had surgery alone

Definitive RT local control rate = 22.6% (comparable to those of other tumor sites treated with definitive RT)

EFS and OS at 5 yrs, 47% and 58%
Local therapy for metastatic disease?

EURO-EWING 99

- Retrospective. 120 patients.
- Primary: Surgery 22%, Surgery + RT 17%, or definitive RT 33%
- Local treatment of mets: Surgery 5%, Surgery + RT 7%, RT 27%. No local therapy in 27%
- 3-year EFS 24%
  - Surgery 25%
  - Surgery + RT 47%
  - RT 23%
  - no local therapy 13%
- 3-year EFS if treatment of primary and met 39% vs either primary or met 17% vs no local therapy 14% (SS)
- Conclusion: Local therapy important for patients with disseminated Ewing sarcoma and should complement systemic treatment whenever possible
POG 8346: Donaldson et al. *IJROBP* 1998

- IFRT equivalent to whole bone (SF) RT for LC?
- n=178, 1983-1988
- Induction chemo: cyclophosphamide/doxorubicin x 12wks (5c)
- Local Tx based on response:
  - PD $\rightarrow$ RT + salvage chemo
  - If CR/PR $\rightarrow$ surgery (if feasible) + PORT if + margins/gross dz
  - RT alone: randomized to IFRT vs SFRT
    - IF 55.8Gy
    - SF 39.6 Gy + 16.2 Gy boost (GTV + 4cm)
- VACA x 50 wks
EBM – POG 8346

No benefit to whole bone RT

- 5yr EFS: SF 37% vs. IF 39%
- 5yr LC: SF 53% vs IF 53%

- Limitations: low accrual, high rate DM
Pelvic tumors: poor prognosis
Primary resection difficult, chemoRT mainstay
Wide en-block resection → ECI 50Gy @ 2Gy/min → debulking of tumor from bone → re-implantation
13 patients, median age 16 yrs, no mets
OS 69%, 9/13 NED at last followup, 4 died of metastatic disease, no local relapse
7/13 with good/excellent functional outcomes

RT Target Volume (AEWS1031)

- RT to entire bone not necessary (POG 8346)
- GTV: pre-chemo bony disease and post-chemo soft tissue disease
- CTV margin of 1-1.5cm
- Make sure scars and drain sites are wired and apply bolus to ensure adequate coverage
- 45 Gy + 10.8 Gy (definitive RT or gross residual)
- 36 Gy (pre-op RT)
- 45-50.4 Gy (post-op RT)
RT Complications

- Bone growth abnormalities
  - > 20 Gy can prematurely close epiphysis
  - > 20-30 Gy can cause permanent lymphedema
  - Limb length discrepancy – 2-6 cm
  - Permanent weakening of bone
    - High risk of fracture within 18 mos of RT
- Dermatitis: recall-reaction w/ ADR and dactinomycin
- Decreased ROM 2/2 joint fibrosis
- Skin hyperpigmentation
- Cystitis (worse w/ cyclophosphamide/ifos)
- Second malignancies (5-10% @ 20yrs → osteosarcoma)
Chemotherapy Regimens

- For non-metastatic disease, standard 5-drug U.S. regimen (VAC + IE)
  - Vincristine
  - Doxorubicin
  - Cyclophosphamide
  - Alternating with ifosfamide and etoposide x 48 weeks
  - Actinomycin sometimes thrown in (VACA+IE)

- For metastatic disease (VAC)
  - Vincristine
  - Doxorubicin
  - Cyclophosphamide
• 342 pts. Localized Ewing's sarcoma of bone, previously untreated
  ○ Group I Institutions: Randomized 3:2 to 1) RT to primary plus VAC + Adriamycin or 2) RT plus VAC
  ○ Group II Institutions: Randomized 3:2 to 3) RT to primary plus VAC and bilateral pulmonary RT (BRP) or 2) RT plus VAC (same as above)
• Chemotherapy given x 6 weeks
  ○ Vincristine and cyclophosphamide q weekly and adriamycin given with the last dose.
  ○ After 6 weeks rest, pts had a 7 week course of continuation therapy that consisted of dactinomycin IV x 5 days followed 9 days later by VCR and cyclophosphamide weekly x 5 weeks. For treatment 1, adriamycin given with the last course in the 7th week of each course.
• RT: entire involved bone to 45-55 Gy (based on age), followed by 10 Gy boost to gross radiographic tumor + soft tissue mass with margin.
  ○ Lung RT: 15-18 Gy given at 150-180 cGy/day.
- 5-yr RFS treatment 1 - 60%, 2 - 24%, 3 - 44%. Similar trend for OS.
  - Worse survival for pelvic sites.
  - 15% LR overall.
  - DM in 1-30%, 2-72%, and 3-42%.
  - BPR was not effective in preventing lung mets.
- Conclusion: improved survival with addition of Adriamycin to VAC.
Non-metastatic pts
- 5-yr EFS 69% vs 54% for VAC+ADR+IE vs VAC+ADR (RR=1.6)
- 5-yr OS 72% vs 61% (RR=1.6)
- Greater reduction in LR than in distant mets. Greater benefit for large primary tumors or pelvic tumors.

For pts with mets, no difference between regimens:
- 5yr EFS 22%
- 5yr OS 34%

Conclusion: improved survival with addition of ifosfamide and etoposide (in non-metastatic pts)
Any benefit to WLI? Toxicity?

99 with pulmonary mets, 70 received WLI,

Local: VAIA +/- etop x14c

- WLI: wk 31, 12-21 Gy +/- boost to thoracic tumor to 54Gy
  - 1.5 Gy QD vs 1.25 Gy BID
  - AP/PA fields

5yr OS:
- 61% (WLI) vs 49% (none)  p=0.36

5yr EFS
- 39% (WLI) vs 37% (none)
WLI- EICRESS 92: Toxicity

<table>
<thead>
<tr>
<th>Late lung toxicity, grade</th>
<th>n</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>mean grade</th>
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<tbody>
<tr>
<td>WLI, no thoracic surgery</td>
<td>16</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>WLI plus thoracic surgery</td>
<td>12</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1.3</td>
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<tr>
<td>All</td>
<td>28</td>
<td>12</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>0.9</td>
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### PFT complications

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<td>43</td>
<td>29</td>
<td>21</td>
<td>7</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age median (range)</th>
<th>≤ 15 Gy</th>
<th>&gt; 15 Gy</th>
<th>Median follow-up (range)</th>
<th>Surgery</th>
<th>EVAIA/VAIA</th>
<th>2nd CTX</th>
<th>3rd CTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without side effects</td>
<td>12</td>
<td>14.7 years (5.6-25.8)</td>
<td>6</td>
<td>6</td>
<td>11.6 months (0.1-151)</td>
<td>4 (33%)</td>
<td>8/4</td>
<td>5 (42%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>With pulmonary function abnormality</td>
<td>16</td>
<td>16.1 years (4.3-34.8)</td>
<td>6</td>
<td>10</td>
<td>32.6 months</td>
<td>8 (50%)</td>
<td>6/10</td>
<td>11 (69%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>All</td>
<td>28</td>
<td>15.0 years (4.3-34.8)</td>
<td>12</td>
<td>16</td>
<td>25.2 months (0.1-151)</td>
<td>12 (43%)</td>
<td>14/14</td>
<td>16 (57%)</td>
<td>9 (34%)</td>
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</table>
Treatment Overview

- **Chemotherapy** is typically given for 12-15 weeks prior to local therapy
  - VAC(A)+/- IE (no IE if metastatic)
- **Local Tx (surgery or radiation therapy or both)**
  - Surgery favored if complete resection is feasible without significant morbidity and functional loss
  - Radiation favored for central lesions (55.8Gy)
- **Radiation**
  - PORT if + margins: 45Gy
  - Definitive RT or PORT w/ gross residual: 55.8Gy
  - Whole lung radiation used for consolidation after chemotherapy (15Gy/10fx), boost residual dz to 45Gy.
    - Can consider resection if <=4 mets
Late (>5yr) recurrences in Ewing’s sarcoma

- >12k childhood cancer survivors
- Overall late relapse 4% and 6% at 10 and 20 years
- Two tumors stood out
  - Ewing’s and CNS tumors
    - 14% at 20 years
- Importance of monitoring 15-20 years from therapy

Wassilewski-Master, JNCI, 2009
What translocation is characteristic of Ewing’s sarcoma?

A. $t(11;22)$  
B. $t(12;16)$  
C. $t(9;22)$  
D. $t(x;18)$  

A
All of the following are true regarding Ewing’s sarcoma, except

A. There is a predilection for whites
B. It is more common among males than females
C. Cytokeratin and neuron-specific enolase can be positive
D. Half of patients present with localized disease at diagnosis

D
• All of the following are true, except
A. Ewing’s sarcoma exhibits chromosomal translocation t(11;22)
B. Codman’s triangle can be observed on radiography
C. Presents more commonly with localized disease than osteosarcoma
D. Radiation plays a prominent role in therapy

C. Ewing’s presents with localized disease 75% of the time, osteosarcoma 90% of the time
In a patient with Ewing’s that has GRD after chemo and surgery, what is the correct RT dose and volume?

A. 45Gy to pre-chemo bone and post-chemo soft tissue tumor
B. 45 Gy to post-chemo bone and post-chemo soft tissue tumor
C. 55.8 Gy to the pre-chemo bone and pre-chemo soft tissue tumor
D. 55.8 Gy to the pre-chemo bone and post-chemo soft tissue tumor

D
All of the following are true regarding IESS-1 in which adria was added to vincristine, actinomycin and cyclophosphamide, except:

A. The addition of adria improved OS
B. The addition of adria improved DFS
C. Pelvic disease sites fared no worse than nonpelvic disease sites
D. Local recurrence did not differ by treatment

C. IESS-1: randomized 335pts to receive adria to VAC + RT (45-55 Gy + 10 Gy boost). Addition of VAC improved both DFS and OS. Pelvic disease sites had poorer survival than nonpelvic (34 vs 57 %). Local recurrence did not differ by treatment
All of the following are true regarding IESS-II in which intermittent high dose was compared to continuous moderate-dose chemo, except:

A. High dose chemo improved OS
B. High dose chemo improved DFS
C. High dose chemo arm had etoposide
D. Cardiac toxicity was worse in high-dose arm

C. IESS-II randomized 214 pt to receive VAC + adria by either moderate-dose continuous or high-dose intermittent regimen. High dose improved OS (77 vs 63%) but with greater cardiotoxicity.
All of the following true regarding IESS-III in which ifosfamide and etoposide were added to VAC + adria, except:

A. The addition of IE improved OS in pts with both metastatic and non-metastatic disease
B. There was a greater reduction in local recurrence than in distant metastasis
C. A quarter of the enrolled patient had metastatic disease
D. There was a greater benefit seen in pelvic tumors

A. IESS-III randomized 518pts to receive IE or not in addition to VAC + adr. 23% of pts had metastatic disease. In non-metastatic pts, addition of IE improved EFS and OS. Greater reduction in local recurrence than distant mets and a greater benefit for large or pelvic tumors. Patients with metastatic disease did not benefit from IE in terms of EFS or OS.
THE END

QUESTIONS?