Local Therapy for Ewing Sarcoma: Current Concepts and Opportunities for Improvement

Safia K. Ahmed, MD
Department of Radiation Oncology
Washington University
August 25, 2017
Outline

• Therapeutic background
• Current local tumor control outcomes
• Identification of patients at higher risk for local failure
• Optimization of local therapy for high risk patients
• Conclusions
Current Treatment Paradigm
Localized Disease

Baseline evaluation → Induction VDC / IE (6 cycles) → Primary tumor local therapy → Consolidation VDC / IE (11 cycles)

VDC / IE = vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide
### Contemporary North American Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>OS</th>
<th>EFS</th>
<th>Local Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT-0091, 1988-1992</td>
<td>VACD, 49 weeks</td>
<td>61.0%</td>
<td>54.0%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>VACD/IE, 49 weeks</td>
<td>72.0%</td>
<td>69.0%</td>
<td>5%</td>
</tr>
<tr>
<td>INT-0154, 1995-1998</td>
<td>VDC/IE, 48 weeks</td>
<td>80.5%</td>
<td>72.1%</td>
<td>6.2%</td>
</tr>
<tr>
<td></td>
<td>VDC/IE, 30 weeks</td>
<td>77.0%</td>
<td>70.1%</td>
<td>5.4%</td>
</tr>
<tr>
<td>AEWS0031, 2001-2005</td>
<td>VDC/IE, q3 weeks</td>
<td>77.0%</td>
<td>65.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td></td>
<td>VDC/IE, q2 weeks</td>
<td>83.0%</td>
<td>73.0%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

85% OS and 75% EFS

VACD = vincristine, doxorubicin, cyclophosphamide, actinomycin D  
VACD/IE = vincristine, doxorubicin, cyclophosphamide, actinomycin D, ifosfamide, etoposide

Granowetter et. al., *J Clin Oncol*, 2009  
Womer et. al., *J Clin Oncol*, 2012
Local Failure
INT-0091, INT-0154, & AEWS0031 Analysis

Ahmed et. al., Int J Rad Bio Phys, 2017 (in press)
“Local tumor control is no longer a problem in the modern era.”

-Medical oncologists
“…similar EFS and OS [between local treatment modalities] reflects the relatively low contribution of local failure to overall disease failure in Ewing Sarcoma.”
Mayo Clinic Ewing Sarcoma Experience

• 500 patient database

• Aims
  • Determine impact of local tumor control
  • Characterize local failure rates across various cohorts
  • Elucidate prognostic variables for local failure
  • Assess importance of local tumor control for metastatic disease
  • Evaluate effect of local treatment modality on patient quality of life
What Is The Impact Of Local Therapy?
Impact of Local Therapy

- Systemic therapy alone: <30% survival

<table>
<thead>
<tr>
<th>Series</th>
<th>5 year post-local relapse survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic</td>
<td>22%</td>
</tr>
<tr>
<td>St. Jude Children’s Research Hospital</td>
<td>21%</td>
</tr>
<tr>
<td>CESS 81, CESS 86, &amp; EICESS 92</td>
<td>24%</td>
</tr>
</tbody>
</table>

Local therapy is a crucial component of the multimodal treatment strategy

CESS = Cooperative Ewing’s Sarcoma Studies
EICESS = European Intergroup Ewing’s Sarcoma Study

Barker et. al., *J Clin Oncol*, 2005
Are All Patient Cohorts Associated With The Same Local Failure Rate?
Local Therapy Approach

- **Definitive surgery**
  - Margin negative resection
  - Minimal morbidity
  - 10% local failure rate

- **Definitive radiotherapy (RT)**
  - Anatomically unfavorable tumors
  - 21% local failure rate

- **Surgery + radiation (S+RT)**
  - Cases of incomplete resection
  - 3% local failure rate
European Outcomes

• CESS 81, CESS 86, & EICESS 92
  • 1981-1999
  • 1,058 patients
  • RT: 26.3%
  • S ± RT: 5.3 - 7.5%

• EURO-EWING99
  • 1998-2009
  • 1,207 patients
  • RT associated with higher local failure rate
  • Await publication

EURO-EWING99 = European Ewing Tumour Working Initiative of National Groups Ewing Tumour Studies 1999
Patient Age
AEWS0031

Womer et. al., *J Clin Oncol*, 2012
Research Article

Adult Ewing Sarcoma: Survival and Local Control Outcomes in 102 Patients with Localized Disease

Safia K. Ahmed, Steven I. Robinson, Scott H. Okuno, Peter S. Rose, and Nadia N. Issa Laack

Local Failure Rate

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>18%</td>
</tr>
<tr>
<td>RT</td>
<td>33%</td>
</tr>
<tr>
<td>S+RT</td>
<td>0%</td>
</tr>
</tbody>
</table>

Ahmed et. al., Sarcoma, 2013
Baldini et. al., Annals of Surgery, 1999
Casey et. al., Radiotherapy and Oncology, 2014
Pretz et. al., Oncologist, 2017
Primary Tumor Site

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>2.0%</td>
</tr>
<tr>
<td>Clavicle</td>
<td>1.5%</td>
</tr>
<tr>
<td>Scapula</td>
<td>4.0%</td>
</tr>
<tr>
<td>Sternum</td>
<td>0.5%</td>
</tr>
<tr>
<td>Ribs</td>
<td>10.0%</td>
</tr>
<tr>
<td>Spine</td>
<td>6.0%</td>
</tr>
<tr>
<td>Pelvis</td>
<td>26.0%</td>
</tr>
</tbody>
</table>

Skeletal: 85%
Extraskeletal: 15%

Ahmed et. al., *Pediatric Radiation Oncology*, 2017 (in press)
Marina et. al., *Sarcoma*, 2015
Pelvis Tumors
AEWS0031

EURO-EWING99: 30% local failure rate

Dirksen et. al., SIOP Annual Meeting, 2016
Womer et. al., J Clin Oncol, 2012
Pelvis Ewing sarcoma: Local control and survival in the modern era

Safia K. Ahmed¹ | Steven I. Robinson² | Carola A. S. Arndt³ | Ivy A. Petersen¹ | Michael G. Haddock¹ | Peter S. Rose³,⁴ | Nadia N. Issa Laack¹

<table>
<thead>
<tr>
<th>Local Failure Rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>19%</td>
</tr>
<tr>
<td>Definitive surgery</td>
<td>13%</td>
</tr>
<tr>
<td>Definitive radiation (RT)</td>
<td>26%</td>
</tr>
<tr>
<td>Surgery + radiation (S+RT)</td>
<td>0%</td>
</tr>
</tbody>
</table>
Pelvis Tumors Treated with RT

Tumor involves L5-S3, right iliac wing, spinal canal, nerves, and soft tissue
12.3 x 8.1 x 6.3 cm

Tumor involves right ilium, acetabulum, superior pubic ramus, vasculature, and soft tissue
15.0 x 13.2 x 9.3 cm
What Clinical Variables Are Prognostic For Local Failure?
Tumor Size

- COG Trials
  - \(< / \geq 8 \text{ cm in maximum dimension}\)
  - INT-0154: No correlation with outcomes
  - IINT-0091 & INT-0154: Tumors \(\geq 8 \text{ cm}\) associated with inferior EFS

- EURO-EWING99
  - Tumors \(\geq 200 \text{ ml}\) associated with higher local failure rate

Andreou et. al., CTOS Annual Meeting, 2016
Dirksen et. al., SIOP Annual Meeting, 2016
Marina et. al., Sarcoma, 2015
Tumor Size
Mayo Clinic Experience

• No correlation with local failure rate by $< / \geq 8$ cm in maximum dimension

• Radiographic response to chemotherapy
  • Partial or complete response: 13%
  • Less than partial response: 36%

Ahmed et. al., Sarcoma, 2013
Prognostic Factors
Pelvis Anatomic Subsites

• Mayo Clinic
  • 36% local recurrence rate for tumors with sacral involvement

• Scandinavian Sarcoma Group
  • Inferior EFS for tumors involving innominate bones
## Prognostic Factors
### Histologic Response to Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Series</th>
<th>Histologic Response</th>
<th>EFS</th>
<th>Local Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CESS 86</td>
<td>≤10% viable tumor cells &gt;10% viable tumor cells</td>
<td>64%</td>
<td>38%</td>
</tr>
<tr>
<td>AEWS0031</td>
<td>&lt;90% necrosis</td>
<td>~65%</td>
<td>~70% ~80%</td>
</tr>
<tr>
<td></td>
<td>≥90% necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No viable tumor cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>≤5% viable tumor cells &gt;5% viable tumor cells</td>
<td>76%</td>
<td>59%</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>≤95% necrosis</td>
<td>36%</td>
<td>44% 9%</td>
</tr>
<tr>
<td></td>
<td>&gt;95% necrosis</td>
<td>74%</td>
<td></td>
</tr>
</tbody>
</table>

Chihak, Ahmed et. al., Manuscript in preparation
Pan et. al., *Int J Rad Onc Bio Phys*, 2015
Paulussen et. al., *J Clin Oncol*, 2001
Womer et. al., CTOS Annual Meeting, 2016
Local Tumor Control
Mayo Clinic Experience

• Cohorts associated with higher local failure rate
  • Patients treated with RT
  • Patients with pelvis tumors

• Prognostic variables
  • Response to neoadjuvant chemotherapy
  • Anatomic subsites

Ahmed et. al., Manuscript in preparation
Can We Validate Our Findings?
COG Local Failure Analysis

• Purpose: To identify clinical and treatment variables associated with higher risk of local failure in Ewing sarcoma patients treated on recent COG protocols

• 956 patients treated with IE based chemotherapy on INT-0091, INT-0154, and AEWS0031 trials
Optimal Local Therapy
COG Local Failure Analysis

RT, 15.3%
HR 4.12, p < 0.01

S+RT, 6.6%
HR 1.69, p = 0.12

Surgery, 3.9%
HR 1.0

Ahmed et. al., Int J Rad Bio Phys, 2017 (in press)
Primary Tumor Site
COG Local Failure Analysis

<table>
<thead>
<tr>
<th>Primary Tumor Site</th>
<th>Local Failure</th>
<th>Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremity</td>
<td>5.4%</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td>Pelvis</td>
<td>13.2%</td>
<td>2.47</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Axial non-spine</td>
<td>5.3%</td>
<td>0.95</td>
<td>0.90</td>
</tr>
<tr>
<td>Spine</td>
<td>3.6%</td>
<td>0.60</td>
<td>0.49</td>
</tr>
<tr>
<td>Extraskeletal</td>
<td>9.1%</td>
<td>1.82</td>
<td>0.08</td>
</tr>
</tbody>
</table>

74%, surgery
49%, RT
53%, surgery
63%, RT
43%, S+RT

Axial non-spine = ribs, scapula, clavicle, sternum

## Primary Tumor Site

### COG Local Failure Analysis

<table>
<thead>
<tr>
<th></th>
<th>Local Failure</th>
<th>Hazard Ratio</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PELVIS TUMORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>3.9%</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>22.4%</td>
<td>6.31</td>
<td>0.01</td>
</tr>
<tr>
<td>S+RT</td>
<td>5.1%</td>
<td>1.31</td>
<td>0.78</td>
</tr>
</tbody>
</table>

**EXTREMITY TUMORS**

<table>
<thead>
<tr>
<th></th>
<th>Local Failure</th>
<th>Hazard Ratio</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>3.7%</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>14.8%</td>
<td>3.99</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>S+RT</td>
<td>5.4%</td>
<td>1.42</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Echoed by EURO-EWING99 analysis
Extremity Tumors Treated with RT

Tumor extends 30.0 cm along the right femur, with a 23.0 x 22.0 x 12.6 cm soft tissue mass

**Tumor Size**

**COG Local Failure Analysis**

- Available in only 40% of cohort

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>RT</th>
<th>S+RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 cm</td>
<td>73 (54%)</td>
<td>42 (31%)</td>
<td>21 (15%)</td>
<td>0.21</td>
</tr>
<tr>
<td>≥8 cm</td>
<td>134 (54.2%)</td>
<td>60 (24.2%)</td>
<td>53 (21.4%)</td>
<td></td>
</tr>
</tbody>
</table>

- No difference in local failure incidence: ~8%

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>RT</th>
<th>S+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 cm</td>
<td>7.2%</td>
<td>12.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>≥8 cm</td>
<td>3.1%</td>
<td>20.0%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>
Tumor Size: All Patients

COG Local Failure Analysis

Tumor Size: RT Patients
COG Local Failure Analysis

Hazard ratio (event: local recurrence) vs. Tumor size (cm)

Tumor Size
1D Measurements Inadequate?

AEWS1031: Evaluate volumetric tumor size as prognostic factor for EFS
Patient Age
COG Local Failure Analysis

≥18 years, 11.9%
HR 1.97, p = 0.02

<18 years, 6.7%
HR 1.0

Local Failure Summary
High Risk Patients

- RT: ~3x higher risk
  - Pelvis tumors: ~6x higher risk
  - Extremity tumors: ~4x higher risk
- Adult patients: ~2x higher risk
- No association with tumor size in maximum dimension

How Can We Optimize Local Tumor Control For Patients At High Risk For Local Failure?
## Histologic Response

<table>
<thead>
<tr>
<th>Series</th>
<th>Histologic Response</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CESS 86</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>AEWS0031</td>
<td>&lt;90% necrosis &lt;br&gt; ≥90% necrosis &lt;br&gt; No viable tumor cells</td>
<td>~65%</td>
<td>~70% &lt;br&gt; ~80%</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>≤5% viable tumor cells &lt;br&gt; &gt;5% viable tumor cells</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>59%</td>
<td></td>
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<td>MD Anderson</td>
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<tr>
<td></td>
<td></td>
<td>74%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Chihak, Ahmed et. al., Manuscript in preparation
Pan et. al., *Int J Rad Onc Bio Phys*, 2015
Paulussen et. al., *J Clin Oncol*, 2001
Womer et. al., CTOS Annual Meeting, 2016
### Histologic Response
#### French EW93

<table>
<thead>
<tr>
<th>Risk group</th>
<th>% residual viable after induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard risk</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>5-29%</td>
</tr>
<tr>
<td>High risk</td>
<td>≥30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Tumor regression ≥ 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
<th>+/- Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Risk</td>
<td>VA/2w x6 + CD/3w x3-6</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>VA/2w x6 + IE/3w x6</td>
</tr>
<tr>
<td>High Risk</td>
<td>IE/3w x2 + Bu/Mel/CSP</td>
</tr>
</tbody>
</table>

**Clinical response and initial tumor volume (ITV):**
- Responders and low ITV ≤ 100 ml
- Responders and high ITV > 100 ml
- Non responders (reduction of initial volume less than 50%)

---

Gaspar et. al., *Eur J Cancer*, 2012
Histologic Response
French EW93

Gaspar et al., *Eur J Cancer*, 2012
Histologic Response

- Potential to determine patients at higher risk of recurrence

- AEWS1031: Evaluate histologic response as prognostic factor for EFS

- Can only be assessed in surgical cases
Radiologic Response

EURO-EWING99: Tumor regression >90% associated with lower local failure rate

Andreou et. al., CTOS Annual Meeting, 2016
Gaspar et. al., Eur J Cancer, 2012
Radiologic Response

• Assessment of soft tissue response sufficient?

• How best to interpret osseous changes?

Garcia-Castellano et. al., Sarcoma, 2011
Radiologic Response
PET/CT

Role for determining high risk RT cases?

Childrensoncologygroup.org
Hawkins et. al., *J Clin Oncol*, 2005
Koshkin et. al., *J Clin Oncol*, 2016
Other Radiologic Assessments
Tumor Hypoxia

• German analysis: Increasing tumor hypoxia associated with increased risk of metastases

• Correlation of tumor hypoxia with local tumor control?

• Hypoxia PET Tracers: $^{18}$F-FDG, $^{18}$F-FMISO, $^{18}$F-FAZA, and $^{64}$Cu-ATSM

Dunst et. al., Strahlenther Onkol, 2006
Other Radiologic Assessments
Advanced MRI Imaging

• Perfusion MRI

• Advanced MR Elastography

• Current Mayo Clinic Protocol: Establish correlation between perfusion MRI, $^{18}$F-FDG PET activity, MRI contrast enhancement, MRE and pathologic response for sarcomas
Other Radiologic Assessments

Radiomics

Aerts et. al., *Nature Communications*, 2014
High Risk Patients
Optimization of Local Tumor Control

- Additional prognostic variables
  - Histologic response for surgical cases
  - Imaging characteristics and response for unresectable cases
- Intensification of local therapy
Intensification of Local Therapy
S+RT

- Local failure incidence similar to surgery and superior to RT despite higher risk cases

<table>
<thead>
<tr>
<th></th>
<th>Local Failure Incidence</th>
<th>Hazard Ratio</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>3.9%</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td>RT</td>
<td>15.3%</td>
<td>4.12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>S+RT</td>
<td>6.6%</td>
<td>1.69</td>
<td>0.12</td>
</tr>
</tbody>
</table>

- Standard of care for majority of high risk soft tissue sarcomas

O'Sullivan et. al., *Lancet*, 2002
S+RT
EURO-EWING99

<table>
<thead>
<tr>
<th>No of local recurrences / No of pts</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORT vs no PORT</td>
<td></td>
</tr>
<tr>
<td>&lt; 14 years</td>
<td>7/60 vs 21/234</td>
</tr>
<tr>
<td>≥ 14 years</td>
<td>6/82 vs 33/223</td>
</tr>
<tr>
<td>Osseous lesion +/- soft</td>
<td>12/123 vs 48/416</td>
</tr>
<tr>
<td>Soft tissue only</td>
<td>1/19 vs 6/41</td>
</tr>
<tr>
<td>Limb</td>
<td>6/47 vs 18/277</td>
</tr>
<tr>
<td>Sacrum or vertebrae</td>
<td>1/16 vs 4/11</td>
</tr>
<tr>
<td>Pelvis other than sacrum</td>
<td>1/23 vs 13/57</td>
</tr>
<tr>
<td>Other axial site</td>
<td>5/56 vs 19/112</td>
</tr>
<tr>
<td>&lt; 200 mL</td>
<td>6/67 vs 26/309</td>
</tr>
<tr>
<td>≥ 200 mL</td>
<td>7/75 vs 28/148</td>
</tr>
<tr>
<td>Complete resection</td>
<td>7/81 vs 46/426</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>6/61 vs 8/31</td>
</tr>
<tr>
<td>Complete necrosis</td>
<td>1/65 vs 35/299</td>
</tr>
<tr>
<td>Incomplete necrosis</td>
<td>12/77 vs 19/156</td>
</tr>
<tr>
<td>Overall</td>
<td>13/142 vs 54/457</td>
</tr>
</tbody>
</table>

subHR(PORT) = 0.43 (95%CI, 0.21-0.88)  
Adjusted subHR (PORT vs no PORT)  
p = 0.02
Functional Outcomes & Quality of Life

- **European Survivorship Study**
  - Survivors returned to normal life with minor limitations
  - 56% received S+RT

- **Mayo Clinic Survivorship Analysis**
  - Local therapy modality does not significantly affect musculoskeletal outcomes or quality of life

Ranft et. al., *J Clin Oncol*, 2017
Preoperative RT?

• Advantageous compared to postoperative RT for soft tissue sarcomas

• Lower dose and more limited treatment volumes

• AEWS1031: 36.0 Gy
## Intensification of Local Therapy
### RT Dose Escalation

<table>
<thead>
<tr>
<th>Series</th>
<th>RT Dose</th>
<th>Local Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>IESS I</td>
<td>&lt;40 Gy</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>≥60 Gy</td>
<td>6%</td>
</tr>
<tr>
<td>Baylor / Methodist Hospital</td>
<td>≤8 cm, &lt;49 Gy</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>≥49 Gy</td>
<td>6.7%</td>
</tr>
<tr>
<td></td>
<td>≥8 cm, &lt;54 Gy</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>≥54 Gy</td>
<td>14.3%</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>&lt;56 Gy</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>≥56 Gy</td>
<td>0%</td>
</tr>
<tr>
<td>St. Jude, Phase II trial</td>
<td>≥8 cm, 64.8 Gy</td>
<td>0%</td>
</tr>
</tbody>
</table>

IESS = Intergroup Ewing’s Sarcoma Study

Ahmed et. al., *Sarcoma*, 2013
Razek et. al., *Cancer*, 1980
RT Dose Escalation
Secondary Sarcoma Risk

Before 1990

Kuttesch et. al., J Clin Oncol, 1996
Secondary Sarcoma Risk
RT Treatment Volume

Early cooperative group trials

Ahmed et. al., Pediatric Radiation Oncology, 2017 (in press)
Razek et. al., Cancer, 1980
RT Dose Escalation
Contemporary Planning Techniques

Doses ~70.0 GyRBE for osteosarcoma, chordoma, and chondrosarcoma
Intensification of Local Therapy
Systemic Agents

EURO-EWING99 R2

Localized disease → VIDE → Either >200 ml tumor or ≥ 10% viable cells → VAI

BuMel with stem cell rescue

VIDE = vincristine, doxorubicin, ifosfamide, etoposide
VAI= vincristine, actinomycin D, ifosfamide
BuMel = busulfan, melphalan

Whelan et. al., ASCO Annual Meeting, 2016
Intensification of Local Therapy
Systemic Agents

• AEWS1031: VDC/IE/VTC

• SARC 028: Pembrolizumab
  • No significant response in bone tumors

• DNA repair pathway inhibitors
  • Ewing sarcoma cells express high levels of DNA replication stress

Childrensoncologygroup.org
Mackintosh et. al., Oncogene, 2013
Nieto-Soler et. al., Oncotarget, 2016
Tawbi et. al., ASCO Annual Meeting, 2016
What Are The Future Directions For Local Therapy In Ewing Sarcoma?
Future Directions

• Comprehensive analysis of pelvis tumors treated on INT-0091, INT-0154, and AEWS0031 trials

• Further characterization of tumors at diagnosis and in response to neoadjuvant chemotherapy with newer imaging techniques

• High risk pilot study
Metastatic Disease

INT-0091
5 year OS

Localized disease 72%
Metastatic disease 34%

Ahmed et. al., Pediatric Radiation Oncology, 2017 (in press)
### Metastatic Disease

#### Local Tumor(s) Control

<table>
<thead>
<tr>
<th>Series</th>
<th>Treatment</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodist</td>
<td>Absence of local therapy to primary site</td>
<td>Median OS: 9 mo</td>
</tr>
<tr>
<td>EURO-EWING99</td>
<td>Absence of local therapy to metastases</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Local therapy to metastases</td>
<td>39%</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Absence of local therapy to all metastases</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Local therapy to all metastases</td>
<td>11%</td>
</tr>
</tbody>
</table>

- **AEWS1221**: SBRT for bone metastases
Conclusions

• Local therapy crucial component of multimodal therapy for Ewing Sarcoma

• Choice of local therapy modality made on a case by case basis

• Current 5 year local failure rates: 3-25%
Conclusions

• Highest risk cohorts for local failure:
  • Patients treated with definitive radiotherapy
    • Especially pelvis and extremity tumors
  • Adult patients
  • Question tumor size
Conclusions

- Additional prognostic factors
  - Alternative to tumor size in maximum dimension
  - New imaging techniques
  - Response to neoadjuvant chemotherapy
Conclusions

• Local therapy intensification for high risk patients
  • S+RT
  • RT dose escalation
  • New systemic agents
  • Local therapy of all metastases
Acknowledgements

• Co-investigators

• Children’s Oncology Group

• Dr. Nadia Laack
Questions & Discussion
### EURO-E.W.I.N.G. 99

<table>
<thead>
<tr>
<th>VIDE x 6</th>
<th>R1</th>
<th>VAIX1</th>
<th>VAC x 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR 1.5  mg/m²/d dl 1</td>
<td>OP, good response (gr)</td>
<td>1.5 mg/m²/d dl</td>
<td>VCR 1.5  mg/m²/d dl</td>
</tr>
<tr>
<td>IFO 3000 mg/m²/d dl1, d2, d3</td>
<td>if early RAD mandatory</td>
<td>0.75 mg/m²/d dl</td>
<td>VAC 0.75 mg/m²/d dl</td>
</tr>
<tr>
<td>DOX 20  mg/m²/d dl1, d2, d3</td>
<td>&lt;200 ml + RAD</td>
<td>CYC 1500 mg/m²/d dl</td>
<td></td>
</tr>
<tr>
<td>ETO 150 mg/m²/d dl1, d2, d3</td>
<td>&lt;200 ml + RAD + OP (gr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### SURGERY

<table>
<thead>
<tr>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP, poor response (pr)</td>
<td>OPTIONS</td>
</tr>
<tr>
<td>if early RAD mandatory</td>
<td>ME-ME</td>
</tr>
<tr>
<td>≥200 ml + RAD +/- OP</td>
<td>Treo-Mel</td>
</tr>
<tr>
<td>&lt;200 ml + RAD + OP (pr)</td>
<td>Bu-Mel*</td>
</tr>
<tr>
<td>lung metastases</td>
<td>Bu-Mel*</td>
</tr>
</tbody>
</table>

#### Register

<table>
<thead>
<tr>
<th>Register</th>
<th>Stratify</th>
<th>Randomise</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBP C</td>
<td>PBP C</td>
<td>R</td>
</tr>
</tbody>
</table>

* inapplicable for previously irradiated central axis sites, off randomisation in R2

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**< Radiotherapy in selected cases**

see protocol for indication

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**MAYO CLINIC**

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