Ewing's Sarcoma
Adjuvant Indications
Role of Radiation – unresectable tumors

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Assoc. Professor
Regional Cancer Centre
Ewing’s sarcoma family of tumors (ESFT)

- Classical Ewing’s sarcoma of the bone
- Extra skeletal Ewing’s sarcoma
- Askin tumor of the thoracic wall
- Peripheral neuro-ectodermal tumor (pPNET)

WHO classification: ES/PNET
ES/PNET – Genetic abnormality

- Rearrangements of **EWSR1** with **FLI1** or **FLI-1 related gene**.
  - Seen in 98%.
    - t(11;22)(q24;q12) → **EWS-FLI** gene seen in 85%
    - t(21;22)(q22;12) → **EWS-ERG** gene seen in 10%

- Ewings like sarcomas
  - BCOR re-arranged sarcoma
  - CIC re-arranged sarcoma  (older age, mean ~30yrs, mostly soft tissue)
ES/PNET – Molecular pathogenesis

Transcriptional activation and repression
Alteration of splice site selection
Modulation of RNA half-life

DOI:10.1038/pr.2012.54
Clinical Presentation

- Pain 90%
- Swelling 80%
- Impaired limb movt 25%
- Neurological 10%
- Fever 5%
- Mets symptoms

Axial skeleton
- Diaphyseal
- Mets to LNs, liver, CNS – v. rare

FIGURE 33.3 Primary tumor and metastatic sites in Ewing sarcoma. Data based on 1,426 patients from European Intergroup Cooperative Ewing Sarcoma Studies (EI-CESS) trials.
• Prognostic factors
  – Metastasis
    • Pulmonary vs Others
  – Site
    • Axial vs Extremity
  – Location, distal better than proximal: failures
    • 5% distal
    • 25% proximal
    • 35% central
  – Size ≤ 8cm better than > 8cm (failure rate 10% vs. 30%)
  – Volume > 200ml
  – Response to chemotherapy
  – Elevated LDH
  – Age > 17 yrs
Workup

• Imaging of primary
  – X-ray
  – CT
  – MRI – preferred
    • superior definition of tumor size, local intraosseous and extraosseous extent, and the relationship of the tumor to fascial planes, vessels, nerves, and organs.
    • Image the entire bone to detect any skip lesions

\[TV = a \times b \times c \times F,\]

where \(a\), \(b\), and \(c\) represent the maximum tumour dimensions in three planes,

with \(F = \pi / 6 = 0.52\) for spherical tumours,

or \(F = \pi / 4 = 0.785\) for cylindrical tumours
Workup

• Biopsy
  – Multiple core Bx or
  – Open, Longitudinal
    • In accordance with planned resection
    • From soft tissue component
    • Drain if needed (avoid hematoma)
IHC

Optimal panels of various IHC antibody markers for individual malignant RCTs are as follows:

- **Ewing sarcoma**: MIC2/CD99 (invariably diffuse, cytoplasmic membranous immunoexpression), NKX2.2, Fli1, Caveolin, coupled with negative expression of LCA.

- **Neuroblastoma**: Synaptophysin, chromogranin, neuron-specific enolase (NSE), and CD56.

- **Non-Hodgkin’s lymphomas**: LCA, CD20, and other lineage specific markers such as CD30 for ALCL (ALK+ or ALK-), Tdt for lymphoblastic lymphoma.

- **Small cell osteosarcoma**: SATB2. Considering a small cell osteosarcoma can be positive for MIC2, similar to Ewing sarcoma, further molecular testing is recommended as Ewing sarcoma is characterized by specific underlying translocations t (11; 22) (EWS-FLI1), in most cases.

- **Plasma cell dyscrasia/myeloma**: CD138 (Syndecan-1), Kappa, and Lambda for evaluating light chain restriction.

- **Rhabdomyosarcoma**: Desmin, MyoD1, Myogenin

- **Mesenchymal chondrosarcoma**: MIC2/CD99 and Leu7. S100 protein highlights the chondroid component.

Rekhi et al. DOI: 10.4103/IJPM.IJPM_675_18
FISH/RT-PCR

- If neg: EWSR1 breakapart probe → ?NGS
Workup

- CT chest

  - Definite
    1 nodule  > 1cm
    >1 nodule  >0.5cm

  - Questionable
    1 nodule  > 0.5-1cm
    >1 nodule  >0.3-0.5cm

  - Suggest Biopsy

- Bone scan

- Bone marrow biopsy
  - As of now: Mandatory
  - Incidence of isolated marrow involvement is rare!!

- Role of PET-CT in replacing Bone marrow biopsy and bone scan, and CT chest?
  - Entire body needs to be covered (not upto just mid-thigh)
  - May be inferior to dedicated CT-chest

EURO EWING 99/2008, COG AEWS0031 Protocols
ES/PNET - Treatment

- Local therapy

- Systemic therapy
Multi-disciplinary treatment

Induction Chemotherapy
- Early metastasis prophylaxis
- Facilitate conservative surgery and/or radiotherapy

Local Control
- Surgery and/or
- Radiotherapy

Maintenance Chemotherapy
- Metastasis prophylaxis
ES/PNET – Evolution of treatment

• Initial documentation of response to Radium
  – MGH (1930-1952)
    – 68% local control
    – 18% 6 yr survival
  – Univ of California (1935-70)
    – 72% local control
    – 24% 5yr survival

No chemotherapy
Whole bone RT
Low voltage X-rays
Tumor dose above 5000 rads.

1970s......multiagent chemotherapy

• IESS -1 (1973-78)
  – 89% local control with 55-65 Gy WB RT
  – 60% 5yr EFS

1968 – Hustu: Combination – V+C & RT- sustained resp-5 pt

Longer survival – c/c toxicities of RT
– apparent & less acceptable.

Surgical advocates – Pritchard
Observational studies – better time
to relapse and OS in IESS-1
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>5yr EFS</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IESS-I (1973-78)</strong></td>
<td>VAC</td>
<td>24%</td>
<td>Value of Doxorubicin. Benefit of WLI?</td>
</tr>
<tr>
<td></td>
<td>VAC+WLI</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VACD</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td><strong>IESS-II (1978-82)</strong></td>
<td>VACD-MD</td>
<td>48%</td>
<td>Value of aggressive cytoreduction</td>
</tr>
<tr>
<td></td>
<td>VACD-HD</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td><strong>UKCCSG/MRC (1978-86)</strong></td>
<td>VACD</td>
<td>41%</td>
<td>Tumor site as prognostic factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axial: 38%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extre: 52%</td>
<td></td>
</tr>
<tr>
<td><strong>CESS-81 (1981-85)</strong></td>
<td>VACD</td>
<td>Local failure</td>
<td>Poor quality RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sx : 6%</td>
<td>Tumor volume &amp; Histologic response as prognostic factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sx+RT: 17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT : 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tmr vol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;100ml : 80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;100ml : 31%</td>
<td></td>
</tr>
<tr>
<td><strong>CESS-86 (1986-91)</strong></td>
<td>&lt;100ml</td>
<td>Local Failure</td>
<td>RT randomised to Conventional (1.8 Gy)</td>
</tr>
<tr>
<td></td>
<td>VACD</td>
<td>Relapse</td>
<td>Hyper# split course (1.6 Gy BD) - No difference</td>
</tr>
<tr>
<td></td>
<td>&gt;100ml</td>
<td>Sx : 4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VAID</td>
<td>Sx : 3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sx+RT : 17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT : 13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sx+RT : 34%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT : 30%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Treatment Details</td>
<td>5yr EFS</td>
<td>Prognostic Factors</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>POG 8346 (1983-88)</strong></td>
<td>SFRT IFRT (tailored) + WBRT (39.6Gy)+Bst(16.2) Only to Boost field (55.8)</td>
<td><strong>5yr EFS</strong></td>
<td>Distal extr : 65% Central : 63% Prox extre : 46% Pelvi-sacral:24%</td>
</tr>
<tr>
<td></td>
<td>No difference in EFS or LC</td>
<td></td>
<td>5yr local control Appropriate RT : 80% Minor deviation: 48% Major deviation: 16%</td>
</tr>
<tr>
<td><strong>1st POG-CCG (INT-0091) (1988-93)</strong></td>
<td>VACD</td>
<td><strong>54%</strong></td>
<td>Localised : IE beneficial Metastatic: IE no benefit</td>
</tr>
<tr>
<td></td>
<td>VACD+IE</td>
<td><strong>69%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>EICESS-92 (1992-99)</strong></td>
<td>SR: VAID vs. VACD HR: VAID vs. EVAID</td>
<td><strong>68% vs. 67%</strong></td>
<td>Prognostic factors -Stage, Histologic response, type of local treatment. C more toxic than I, E beneficial in HR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>44% vs. 52%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>2nd POG-CCG (INT-0154) (1995-98)</strong></td>
<td>VCD+IE</td>
<td><strong>72%</strong></td>
<td>No benefit of high-dose alkylating agent</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>70%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>1st COG (AEWS0031) (2001-05)</strong></td>
<td>VCD+IE (Q3w) vs. (Q2w)</td>
<td><strong>65% (4yr)</strong></td>
<td>Dose compression better</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>76%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Euro-Ewing 99</strong></td>
<td></td>
<td></td>
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</tr>
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</table>
Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children’s Oncology Group

Richard B. Womer, Daniel C. West, Mark D. Krailo, Paul S. Dickman, Bruce R. Pawel, Holcombe E. Grier,

Fig 1. Kaplan-Meier plots of treatment outcome. (A) Event-free survival (EFS) according to the assigned treatment regimen. (B) Overall survival (OS) by regimen. (C) EFS and (D) OS, respectively, for the four strata, pooling the treatment regimens.
HD Chemo, SC support
EURO EWING 99,2008

**VIDE**
- Vincristine 1.5mg/m² D1
- Ifosfamide 3g/m² D1-3
- Doxorubicin 20mg/m² D1-3
- Etoposide 150mg/m² D1-3

**VAI**
- Vincristine 1.5mg/m² D1
- Actinomycin D 0.75mg/m² D1-2
- Ifosfamide 3g/m² D1-2

**Poor histological response ≥ 10% residual viable cells**
- Surgery after induction chemotherapy alone

**Large tumour ≥200ml**
- Surgery after chemo and early radiation therapy
- Initial surgery
- Late radiation therapy

**BuMel**
- Busulfan 16mg/kg over 4 days
- Melphalan 140 mg/m² D5

Jeremy Whelan, Marie-Cécile Le Deley, Uta Dirksen, Gwénaël Le Teuff, Bernadette Brennan, Nathalie Gaspar,

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Radiation Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralesional surgery</td>
<td>54.4</td>
</tr>
<tr>
<td>Marginal surgery with poor histological response (≥10% residual tumour cells)</td>
<td>54.4</td>
</tr>
<tr>
<td>Marginal surgery with good histological response (&lt;10% residual tumour cells)</td>
<td>44.8</td>
</tr>
<tr>
<td>Wide resection with poor histological response (≥10% residual tumour cells)</td>
<td>44.8</td>
</tr>
</tbody>
</table>

![Event-Free Survival Graph](image1)

![Overall Survival Graph](image2)
Local treatment

• Attain complete tumor eradication
• Maximising function and cosmesis
• Minimising long term morbidity
RT vs. Sx

No randomised trials – no direct comparison
Many retrospective series – local control improves when surgery is possible.

Radiotherapy  
• Site : Unfavourable  
• Volume: Bulky  
• Inoperable

Surgery  
• Site : Favourable  
• Volume: Less bulky  
• Operable - expendable
Table 5.15 Results of radiotherapy for Ewing’s sarcoma

<table>
<thead>
<tr>
<th>Institution</th>
<th>Years</th>
<th>No. of patients</th>
<th>Chemotherapy agents</th>
<th>Radiation dose</th>
<th>Volume</th>
<th>Local control</th>
<th>5-year EFS/DFS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH</td>
<td>1930–1952</td>
<td>22</td>
<td>None</td>
<td>2000–6000 r</td>
<td>WB</td>
<td>68%</td>
<td>18%</td>
<td>Wang et al.1</td>
</tr>
<tr>
<td>UCSF</td>
<td>1945–1965</td>
<td>20</td>
<td>None</td>
<td>16–65 Gy</td>
<td>WB</td>
<td>72%</td>
<td>25%</td>
<td>Phillips and Sheline2</td>
</tr>
<tr>
<td>IESS-I</td>
<td>1973–1978</td>
<td>148*</td>
<td>VACA</td>
<td>55–65 Gy</td>
<td>WB</td>
<td>89%</td>
<td>60%*</td>
<td>Nesbit and Rosen71</td>
</tr>
<tr>
<td>IESS-II</td>
<td>1978–1982</td>
<td>108†</td>
<td>VACA</td>
<td>55 Gy</td>
<td>WB</td>
<td>93%</td>
<td>73%†</td>
<td>Burgert et al.175</td>
</tr>
<tr>
<td>CESS-I</td>
<td>1981–1985</td>
<td>32</td>
<td>VACA</td>
<td>45–60 Gy</td>
<td>WB</td>
<td>54%a</td>
<td>44%</td>
<td>Sauer et al.158</td>
</tr>
<tr>
<td>CESS-II</td>
<td>1986–1991</td>
<td>44</td>
<td>VACA/VAIA</td>
<td>60 Gy</td>
<td>PB</td>
<td>86%</td>
<td>70%</td>
<td>Dunest et al.177</td>
</tr>
<tr>
<td>St Jude</td>
<td>1978–1988</td>
<td>43</td>
<td>VA/CA/BCNU</td>
<td>30–60 Gy</td>
<td>PB</td>
<td>58%b</td>
<td>53%</td>
<td>Arai et al.155</td>
</tr>
<tr>
<td>NCI</td>
<td>1968–1980</td>
<td>107</td>
<td>VC/VAC/VADRIAC</td>
<td>50 Gy</td>
<td>WB</td>
<td>80%</td>
<td>29%</td>
<td>Kinsella et al.163</td>
</tr>
<tr>
<td>NCI</td>
<td>1986–1992</td>
<td>46</td>
<td>VADRIAC/IE</td>
<td>26–63 Gy</td>
<td>N/A</td>
<td>80%</td>
<td>42%</td>
<td>Wexler et al.165</td>
</tr>
<tr>
<td>Chile</td>
<td>1986–1991</td>
<td>11</td>
<td>VACA</td>
<td>45–63 Gy</td>
<td>PB</td>
<td>73%</td>
<td>36%</td>
<td>Villareall et al.161</td>
</tr>
<tr>
<td>Scandinavia</td>
<td>1984–1990</td>
<td>17</td>
<td>VACAMB</td>
<td>40–60 Gy</td>
<td>N/A</td>
<td>76%</td>
<td>35%</td>
<td>Nilbert et al.161</td>
</tr>
<tr>
<td>Bologna</td>
<td>1972–1987</td>
<td>62</td>
<td>VA/VA</td>
<td>35–60 Gy</td>
<td>WB/PB</td>
<td>77–81%</td>
<td>N/A</td>
<td>Toni et al.154</td>
</tr>
<tr>
<td>University of Florida</td>
<td>1971–1990</td>
<td>31</td>
<td>VADRIAC</td>
<td>50–68 Gy</td>
<td>WB/PB</td>
<td>65%</td>
<td>41%</td>
<td>Bolek et al.166</td>
</tr>
<tr>
<td>POG 8346</td>
<td>1983–1988</td>
<td>94</td>
<td>AC/VAC/VACA</td>
<td>55.8 Gy</td>
<td>WB/PB</td>
<td></td>
<td></td>
<td>Donaldson et al.157</td>
</tr>
</tbody>
</table>

Table 5.14 Local control following resection ± radiation for extremity Ewing’s sarcoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Institution</th>
<th>No. of patients</th>
<th>Local control</th>
<th>5-year survival, DFS, RFS</th>
<th>Preoperative/postoperative radiotherapy</th>
<th>Amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkins</td>
<td>Mayo</td>
<td>27</td>
<td>96% (26/27)</td>
<td>74%</td>
<td></td>
<td>5/27 (18.5%)</td>
</tr>
<tr>
<td>Sauer</td>
<td>CESS-I</td>
<td>60</td>
<td>90% (54/60)</td>
<td>64%</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>Sailer</td>
<td>MGH</td>
<td>12</td>
<td>100%</td>
<td>92%</td>
<td></td>
<td>1/12 (8%)</td>
</tr>
<tr>
<td>Hayes</td>
<td>St Jude</td>
<td>11</td>
<td>100%</td>
<td>80%*</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>Arai</td>
<td>St Jude</td>
<td>17</td>
<td>100%</td>
<td>75%</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>Toni</td>
<td>Bologna</td>
<td>69</td>
<td>96%</td>
<td>59%</td>
<td></td>
<td>13/69 (19%)</td>
</tr>
<tr>
<td>Dunst</td>
<td>CESS-II</td>
<td>132</td>
<td>96%</td>
<td>70%</td>
<td></td>
<td>63/91 (69%)</td>
</tr>
<tr>
<td>Terekii</td>
<td>Brown University</td>
<td>22</td>
<td>95%</td>
<td>41%</td>
<td></td>
<td>13/22 (59%)</td>
</tr>
<tr>
<td>Villoreall</td>
<td>Chile</td>
<td>16</td>
<td>100%</td>
<td>50% (7-year)</td>
<td></td>
<td>50%</td>
</tr>
</tbody>
</table>

*This survival estimate is for all treated patients. Only two relapses occurred among the 11 patients treated with surgery alone as the local treatment. ND = Not described; DFS = disease-free survival; RFS = relapse-free survival.
Patients who underwent surgery were
- younger (P5.02) and had
- more appendicular tumors (P<.001).

Compared with surgery, radiation had higher unadjusted risks of
- any event (HR, 1.70; 95%CI, 1.18-2.44),
- death (HR, 1.84; 95% CI, 1.18-2.85), and
- local failure (HR, 2.57; 95% CI, 1.37-4.83).

On multivariate analysis, compared with surgery, radiation had a
- higher risk of local failure (HR, 2.41; 95% CI, 1.24-4.68), although there
- no significant differences in
  - EFS (HR, 1.42; 95% CI, 0.94-2.14),
  - overall survival (HR, 1.37; 95% CI, 0.83-2.26), or
  - distant failure (HR, 1.13; 95% CI, 0.70-1.84)

These data support surgical resection when appropriate, whereas radiotherapy remains a reasonable alternative in selected patients.
Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group

Safia K. Ahmed, MD

Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Sx (502) 52%</th>
<th>RT (226) 24%</th>
<th>Sx+RT (228) 24%</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT-0091</td>
<td>164 (17.2)</td>
<td>65 (40)</td>
<td>64 (39)</td>
<td>35 (21)</td>
</tr>
<tr>
<td>INT-0154</td>
<td>333 (34.8)</td>
<td>208 (62)</td>
<td>69 (21)</td>
<td>56 (17)</td>
</tr>
<tr>
<td>AEWS0031</td>
<td>459 (48)</td>
<td>229 (50)</td>
<td>93 (20)</td>
<td>137 (30)</td>
</tr>
<tr>
<td>Extremity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>51 (29)</td>
<td>86 (49)</td>
<td>39 (22)</td>
<td></td>
</tr>
</tbody>
</table>

Local failure rate: Overall: 7.3%
Significantly higher in:
1. Age ≥ 18 yrs: 11.9%
2. Pelvic subsite: 13.2%
3. Radiation: 15.3%
• **Surgery**
  – Resectable lesions arising from dispensable bones, or reconstruction / prosthesis feasible.
    • Better local control (?) Doubtful benefit in EFS
    • Avoid RT induced 2nd malignancy
    • In skeletally immature child – prevent long term morbidity, disfigurement
    • Analyze degree of necrosis – prognosis estimation.

    • Site: Dispensable - Fibula, ribs, distal extremities, ileum, body of scapula.
      Reconstruction – Proximal extremities (long bones, tibia, ulna)

• **Radiotherapy**
  – Lack function preserving surgery. (Better function preservation)
  – Inoperable
    • Site: Scapula, pelvis around acetabulum, vertebra, skull, facial bones
Eradication vs. function vs. morbidity

Local treatment individualised based on

- Site
- Size
- Operability
- Age
- Individual preference

No benefit of intra-lesional excision + post-op RT vs. Radical RT
Surgery

Would it be possible to perform a wide excision with adequate margins?
• If No, how to proceed
  – GO ahead with surgery?
  – RT and then surgery?
  – Radical RT?

What structures need to be excised?
• Only residual disease – soft tissue component, involved bone?
• Previously involved muscles also?

Is PORT anticipated?

What would be the expected morbidity?
• Immediate
• Long term
Assessing Margins of Resection

• What is considered adequate margin?
  – Bone margin
    • Bone margin: 2 to 5 cm
      – 1cm may be adequate
  – Soft tissue Margin
    • Fat, muscle: 5 mm
    • Fascia, periosteum and intermuscular septa: 2 mm
Pathological response assessment

• What method do you use?
  – Huvos or modified Huvos
  – CCG / POG grading scheme
  – Salzer-Kuntschik
### HUVOS grading scheme

<table>
<thead>
<tr>
<th>Necrosis (%)</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No necrosis</td>
<td>I</td>
<td>No Rx effect</td>
</tr>
<tr>
<td>&lt;50% necrosis</td>
<td>IIA</td>
<td>Partial/Low</td>
</tr>
<tr>
<td>50-95% necrosis</td>
<td>IIB</td>
<td>Partial/high</td>
</tr>
<tr>
<td>96-99% necrosis</td>
<td>III</td>
<td>Scattered viable foci</td>
</tr>
<tr>
<td>100% necrosis</td>
<td>IV</td>
<td>No viable tissue</td>
</tr>
</tbody>
</table>

### CCG / POG grading scheme

<table>
<thead>
<tr>
<th>Necrosis (%)</th>
<th>Grade</th>
<th>3 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No chemo effect</td>
<td>I</td>
<td>30%</td>
</tr>
<tr>
<td>1-10% necrosis</td>
<td>IIA</td>
<td>30%</td>
</tr>
<tr>
<td>11-90% necrosis</td>
<td>IIB</td>
<td>49%</td>
</tr>
<tr>
<td>91-99% necrosis</td>
<td>III</td>
<td>73%</td>
</tr>
<tr>
<td>100% necrosis</td>
<td>IV</td>
<td>100%</td>
</tr>
</tbody>
</table>

Any issues in assessing tumor response for Ewing ??

Ref: Protocol for the Examination of Specimens From Patients With Primitive Neuroectodermal Tumor (PNET)/Ewing Sarcoma (ES) © 2012 College of American Pathologists (CAP).
• **Issues in assessing tumor response**
  
  – the evaluation of percentage necrosis in ES can be difficult, because unlike osteosarcoma, there is no residual acellular osteoid framework left to demarcate the original tumor bed.
  
  – Ewing cells disappear completely, dramatic volume reduction – necrosis % maybe erroneous.
  
  – Furthermore, data regarding correlation of necrosis with outcome in extraosseous ES is not available.
  
  – Currently, histologic assessment of percentage necrosis is not used formally to guide therapy in ES
## Histologic Response

<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</td>
<td>64%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>&gt;10% viable tumor cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEWS0031</td>
<td>&lt;90% necrosis</td>
<td>~65%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥90% necrosis</td>
<td>~70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No viable tumor cells</td>
<td>~80%</td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>≤5% viable tumor cells</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5% viable tumor cells</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>MD Anderson</td>
<td>≤95% necrosis</td>
<td>36%</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>&gt;95% necrosis</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

Slide courtesy: Ahmed S, Mayo Clinic 2017
Radiological response assessment
Investigational

- MRI
  - Is soft tissue response assessment sufficient?

Prognostic Factors and Patterns of Relapse in Ewing Sarcoma Patients Treated With Chemotherapy and R0 Resection

CONCLUSIONS—Histologic and radiologic response to chemotherapy were independent predictors of outcome. Additional study is needed to determine the role of adjuvant RT for patients who have poor histologic response after R0 resection.

-Pan, Mahajan, IJROBP 2015 June.
Radiologic Response

Tumor regression ≥ 50%
- EFS: 63%

Tumor regression < 50%
- EFS: 50%

+/- Radiotherapy

Standard Risk: VA/2w x6 + CD/3w x3-6
Intermediate Risk: VA/2w x6 + IE/3w x6
High Risk: IE/3w x2 + Bu/Mel/CSP

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

Andreu et. al., CTOS Annual Meeting, 2016
Gaspar et. al., Eur J Cancer, 2012

Slide courtesy: Ahmed S, Mayo Clinic 2017
SUV at diagnosis was significantly lower in patients with good histological response than in patients with poor histological response.

The positive predictive value of an SUV II ≤ 2.5 for favorable response was 84.21 %, and the median SUV II was significantly higher in patients with disease progression (2.3 vs. 1.6, p = 0.04)
Radiotherapy

• Indications
  – Definitive Radiotherapy
  – Post-op adjuvant RT
  – ? Pre-op RT
  – Metastatic
Radical Radiotherapy

• Indication
  – Surgery not feasible
    • Axial site: Spine, Pelvis around the acetabulum, skull/facial bones
    • Extremity: Limb preservation not feasible.
  – Margin negative resection not feasible.
Post-op RT

- Indication
  - Gross or microscopic positive margin
  - Poor histologic response to chemo (European)
  - Pre treatment fracture, hematoma, tissue violation (S Laskar, ICRO 2015)

### ENNEKING CLASSIFICATION OF SURGICAL INTERVENTION

<table>
<thead>
<tr>
<th>Surgical Intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralosional resection</td>
<td>Tumor opened during surgery, or surgical field contaminated, or microscopic or macroscopic residual disease</td>
</tr>
<tr>
<td>Marginal resection</td>
<td>Tumor removed <em>en bloc</em>; however, resection through the pseudocapsule of the tumor; microscopic residual disease likely</td>
</tr>
<tr>
<td>Wide resection</td>
<td>Tumor and its pseudocapsule removed <em>en bloc</em>, surrounded by healthy tissue, within the tumor-bearing compartment</td>
</tr>
<tr>
<td>Radical resection</td>
<td>The whole tumor-bearing compartment is removed <em>en bloc</em>, for example, above-knee amputation in lower leg tumor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations on Post-Operative RT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Gross or microscopic positive margins</td>
</tr>
<tr>
<td></td>
<td>Clear margins but poor histopathological response to chemotherapy (necrosis &lt;90% is the suggested minimum threshold, but &lt;95–99% may be used based on institutional practice)</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>Within 6–8 weeks of surgery (though there is no evidence to suggest that a further delay leads to inferior outcomes)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>45 Gy to the pre-chemotherapy volume</td>
</tr>
<tr>
<td></td>
<td>10.8 Gy boost to areas of gross tumor residual</td>
</tr>
<tr>
<td><strong>Fractionation</strong></td>
<td>Standard daily fractionation of 1.8 Gy per fraction</td>
</tr>
<tr>
<td></td>
<td>Hyperfractionated RT (with equivalent total dose) may be used to reduce long term side effects</td>
</tr>
<tr>
<td><strong>Target volume</strong></td>
<td>Initial phase (45 Gy): pre-chemotherapy tumor volume on MRI with 1.5–2 cm margins. Appropriate modifications should be made in tumors expanding into cavities or the lung</td>
</tr>
<tr>
<td></td>
<td>Boost phase (10.8 Gy): post-operative gross residual disease with 1.5–2 cm margins</td>
</tr>
</tbody>
</table>
• Inadequate surgical margins.

Role of Surgical Margins, in 512 pts (Italy) - Bacci et al, IJROBP 2006

Conclusions: Surgery is better than radiotherapy in cases of extremity ESFT with achievable adequate surgical margins, and in cases of inadequate surgical margins, adjuvant reduced-dose radiotherapy is ineffective. Therefore, when inadequate margins are expected, patients are better treated with full-dose radiotherapy from the start. © 2006 Elsevier Inc.

Implication: Inadequate margin requires more than 45 Gy. When inadequate margin expected – radical RT is a good option, also pre-op RT.

Local therapy in Ewings, 1058 pts, CESS 81,86, EICESS 92 – Schuck et al, IJROBP 2003

Results: The rate of local failure was 7.5% after surgery with or without postoperative RT, and was 5.3% after preoperative and 26.3% after definitive RT \( (p = 0.001) \). Event-free survival was reduced after definitive RT \( (p = 0.0001) \). Irradiated patients represented a negatively selected population with unfavorable tumor sites. Definitive RT showed comparable local control to that of postoperative RT after intralesional resections. Patients with postoperative RT had improved local control after intralesional resections and in tumors with wide resection and poor histologic response compared with patients receiving surgery alone. Patients with marginal resections with or without postoperative radiotherapy showed comparable local control, yet the number of patients with good histologic response was higher in the latter treatment group \( (72.2\% \text{ vs. } 38.5\%) \).

Conclusion: Patients with resectable tumors after initial chemotherapy had a low local failure rate. With preoperative RT, local control was comparable. RT is indicated to avoid intralesional resections. After intralesional or marginal resections and after a poor histologic response and wide resection, postoperative RT may improve local control. © 2003 Elsevier Science Inc.
- Adjuvant PORT in poor responder?

Table 4. Local and combined local and systemic relapses according to combined tumor or treatment characteristics

<table>
<thead>
<tr>
<th></th>
<th>Definitive RT</th>
<th>Preoperative RT</th>
<th>Surgery with or without postoperative RT</th>
<th>Surgery without postoperative RT</th>
<th>Surgery with postoperative RT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extremity tumor (cm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>10/36 (27.7)</td>
<td>1/56 (1.7)</td>
<td>3/110 (2.7)</td>
<td>3/64 (4.6)</td>
<td>0/46 (0)</td>
</tr>
<tr>
<td>≥100</td>
<td>11/31 (35.4)</td>
<td>2/67 (2.9)</td>
<td>1/159 (0.6)</td>
<td>0/88 (0)</td>
<td>1/71 (1.4)</td>
</tr>
<tr>
<td><strong>Central tumor (cm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>7/57 (12.3)</td>
<td>1/29 (3.4)</td>
<td>9/62 (14.5)</td>
<td>2/18 (11.1)</td>
<td>7/44 (15.9)</td>
</tr>
<tr>
<td>≥100</td>
<td>28/106 (26.4)</td>
<td>8/83 (9.6)</td>
<td>20/155 (12.9)</td>
<td>3/45 (6.6)</td>
<td>17/110 (15.4)</td>
</tr>
<tr>
<td>Wide resection and good</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>histologic response</td>
<td>—</td>
<td>—</td>
<td>6/190 (3.1)</td>
<td>1/101 (1)</td>
<td>5/89 (5.6)</td>
</tr>
<tr>
<td>Wide resection and poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>histologic response</td>
<td>—</td>
<td>—</td>
<td>6/84 (7.1)</td>
<td>3/25 (12)</td>
<td>3/59 (5.0)</td>
</tr>
</tbody>
</table>

CLINICAL INVESTIGATION

LOCAL THERAPY IN LOCALIZED EWING TUMORS: RESULTS OF 1058 PATIENTS TREATED IN THE CESS 81, CESS 86, AND EICES 92 TRIALS

Andreas Schuck, M.D.,* Susanne Ahrens, B.S.,† Michael Paulusseen, M.D.,†

• Adjuvant radiation
  – Role in complete pathological response?

Results: One hundred forty-two (24%) of the 599 patients included from 1999 to 2009 received PORT (median dose: 45 Grays). With median follow-up of 6.2 years, 67 patients had an LR (with concomitant metastases in 28), leading to an 8-year LR-incidence = 11.9% (standard error [se] = 1.4%). Overall survival (OS) = 21%. 3 years after LR (31% in isolated LR). Controlling for possible confounders, we observed a statistically significant reduction of LR in patients treated by surgery + PORT compared to surgery alone (subdistribution-hazard ratio = 0.45; 95% confidence interval 0.21–0.88, p = 0.02). The benefit of PORT was particularly marked for tumours larger than 200 ml at diagnosis and 100% necrosis. We observed a non-significant trend for benefit associated with PORT for disease-free, event-free and OS.

Conclusion: Radiotherapy appears to improve local control. We now recommend PORT in case of incomplete removal of the tissues involved by the pre-chemotherapy tumour volume. Further studies are required to assess the balance between benefit and risks.
subHR\textsubscript{(PORT)} = 0.43 (95%CI, 0.21-0.88)
\textit{p} = 0.02
## PORT – RT Dose

<table>
<thead>
<tr>
<th>Margin negative</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor response</td>
<td></td>
</tr>
<tr>
<td>Bulky disease, good response</td>
<td></td>
</tr>
<tr>
<td>Bulky disease, poor response</td>
<td></td>
</tr>
<tr>
<td>R1 resection</td>
<td>Good response</td>
</tr>
<tr>
<td></td>
<td>Poor response</td>
</tr>
<tr>
<td>R2 resection</td>
<td>Good response</td>
</tr>
<tr>
<td></td>
<td>Poor response</td>
</tr>
</tbody>
</table>

### European

<table>
<thead>
<tr>
<th>Surg. margins</th>
<th>Necrosis 100 %</th>
<th>Necrosis &lt;100 %</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>NO RT</td>
<td>45 Gy</td>
<td>----</td>
</tr>
<tr>
<td>Close (&lt; 1cm)</td>
<td>45 Gy</td>
<td>50 Gy</td>
<td>5.4 Gy</td>
</tr>
<tr>
<td>Micro R1</td>
<td>45 Gy</td>
<td>50 Gy</td>
<td>5.4 Gy</td>
</tr>
<tr>
<td>Gross R2</td>
<td>50 Gy</td>
<td>55 Gy</td>
<td>5.4-10-8</td>
</tr>
</tbody>
</table>
**Definitely** PORT

- Positive margin/Gross
- Poor responder

**Definitely** No RT

- Limb tumor < 200ml
- Clear surgical margins
- Complete necrosis

??

- Pelvis subsite
- Bulky, >200ml
- Incomplete removal of involved soft tissue
Pre-op RT

– Would it be possible to perform a wide excision with adequate margins?
  • If No, how to proceed
    – GO ahead with surgery?
    – RT and then surgery?
    – Radical RT?

Low-dose (36.0 Gy) preoperative RT was encouraged on AEWS1031 as a method to improve local tumor control for large pelvis tumors. The results of this study are still pending.

AEWS1031

Preoperative radiotherapy (44.8 Gy) was recommended when there was < 50% reduction of a soft tissue component, evident on repeat imaging after 2 chemotherapy courses. Radiotherapy undertaken whenever possible.

EURO EWING99
-Whelan et al, Clin Sarcoma Res 2018

No benefit of intra-lesional excision+ post-op RT vs. Radical RT
Target Volume

- 94 pts received radical RT
  - 40 pts randomized to Whole bone (standard field) vs. Involved field (Tailored field RT)
  - Standard field: Whole bone (39.6 Gy) + Boost to initial tumor with 2cm margin (upto 55.8 Gy)
  - Tailored field: Initial tumor with 2cm margin
  - 5yr EFS
    - Whole bone: 37%
    - Involved field: 39%

- Subsequently adopted in the next POG-CCG trial (INT 0091)
Target Volume

• Phase I (45 Gy / 25# / 5 wks)
  – Pre-chemotherapy tumor volume on MRI + 1.5-3cm longitudinal margin
  – Appropriate modifications into cavities / lung
  – Include scar if post-op

• Phase II (10.8 Gy / 6# / 2 wks)
  – Post-operative / Post – Chemo residual disease + 1.5-2cm margin
EURO EWING99

Axial
GTV: Pretreatment extent
Safety margin: 2cm margin all around

Extremity
GTV: Pretreatment extent
Safety margin: 3-5cm proximal&distal and 2cm other directions
Boost volume
2cm proximal&distal, 1-2cm other directions

AEWS1031

GTV: Prechemo bony disease and Post chemo soft tissue
CTV: Margin of 1-1.5cm (covering biopsy site/drain site)

Ongoing...Not sure if it is safe !!


GTV1: Pretreatment tumor
CTV1+PTV1: 2-2.5cm margin

GTV2: Postchemo volume
CTV2+PTV2: 1.5-2cm margin

AEWS slide courtesy: Nima Nabavizadeh
RT Dose

- Radical intent
  - 55-60 Gy

- Post-op
  - Close or R1: 50.4 Gy
  - R2: 55.8 Gy

- Pre-op
  - 36-45 Gy to Pre-chemo volume

- Vertebral lesions
  - 45 Gy

<table>
<thead>
<tr>
<th>Surg. margins</th>
<th>Necrosis 100%</th>
<th>Necrosis &lt;100%</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>NO RT</td>
<td>45 Gy</td>
<td>----</td>
</tr>
<tr>
<td>Close (&lt; 1cm)</td>
<td>45 Gy</td>
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<td>5.4 Gy</td>
</tr>
<tr>
<td>Micro R1</td>
<td>45 Gy</td>
<td>50 Gy</td>
<td>5.4 Gy</td>
</tr>
<tr>
<td>Gross R2</td>
<td>50 Gy</td>
<td>55 Gy</td>
<td>5.4-10-8</td>
</tr>
</tbody>
</table>

Data from the University of Florida suggest that hyperfractionated RT (1.2 Gy twice daily with a six hour interfraction interval) may be associated with less long-term toxicity.
RT dose escalation

FP019 SIOP19-0483 Radiotherapy Dose Escalation in Unresectable Ewing's Sarcoma/PNET: Final Results of a Single Institute Phase III Randomized Controlled Trial (SIOP -19 abstract)
Dr Laskar, et al TMH

- Following induction Chemotherapy patients were randomised between
  - standard dose RT (SDRT: 55.8Gy/31 fractions) vs.
  - escalated dose RT (EDRT: 70.2Gy/39 fractions delivered in two phases:
    - Phase I - 55.8Gy/31 fractions followed by Phase II - 14.4Gy/8 fractions boost to the post-induction chemotherapy (CTh) volume
    - LC was significantly superior in EDRT as compared to SDRT (79.2% vs 55.3%, p=0.02).
    - Difference in EFS (29.8% vs 43.8%, p=0.20) and OS (40.4% vs 62.5%, p=0.08) were not significant

https://doi.org/10.1002/pbc.27989
ASTRO 2019
RT dose escalation

Pelvis Ewing sarcoma: Local control and survival in the modern era
Safia K. Ahmed, Mayo Clinic  2017, DOI: 10.1002/pbc.26504

• The 5-year cumulative incidence of local recurrence was 19%, with a
  – 26% incidence for radiation,
  – 13% for surgery, and
  – 0% for surgery + radiation ($P = 0.54$).

• Patients treated with definitive radiation doses $\geq 5,600$ cGy had a lower
  incidence of local recurrence (17% vs. 28%, $P = 0.61$).

• Though statistically not significant, surgery + radiation and definitive
  radiation dose $\geq 5,600$ cGy were associated with the lowest incidence of
  local failure, suggesting treatment intensification may improve local
  control for pelvis ES.

Higher dose – may be beneficial. However it Needs validation
Timing of Local treatment

• Ideally @ 12 weeks.

• Is delay detrimental?
  – For every increase of 4 weeks, the risk of an event increased by
    • 27% for pre-op RT (HR 1.27, 95% CI 1.05–1.53)
    • 14% for Sx+-RT (HR 1.14, 95% CI 1.02–1.27)
    • 7% for RT (HR 1.07, 95% CI 0.96–1.19)
  – Analysis of EICESS 92

– Patients initiating local therapy at
  • 6 to 15 weeks versus 5yr OS of 78.7% 10-year OS 70.3%
  • ≥16 weeks 5yr OS of 70.4% 57.1%, (P < .001).
  • The difference in OS according to time to local therapy was particularly more important in patients receiving radiation therapy alone
  – NCD analysis

Ewings – chest wall

• Indications for hemithorax RT
  – Initial pleural effusion
  – Pleural infiltration
  – Intraoperative contamination?

• Dose: 15 Gy/10#
Survival is influenced by approaches to local treatment of Ewing sarcoma within an international randomised controlled trial: analysis of EICESS-92

- UK - More extremity, fewer central
- Most UK pts had single modality
  - Single (72%)
    - Central $\rightarrow$ RT
    - Extremity $\rightarrow$ Sx
- Most German had multimodality
  - Single (40%)

<table>
<thead>
<tr>
<th></th>
<th>CCLG</th>
<th>GPOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>62%</td>
<td>32%</td>
</tr>
<tr>
<td>Sx</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Sx+RT</td>
<td>11%</td>
<td>56%</td>
</tr>
<tr>
<td>Extremity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>24%</td>
<td>6%</td>
</tr>
<tr>
<td>Sx</td>
<td>47%</td>
<td>25%</td>
</tr>
<tr>
<td>Sx+RT</td>
<td>23%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Table: Treatment modalities

- Surgery alone
- Radiotherapy alone
- Radiotherapy then surgery
- Surgery then radiotherapy
- None (progressive disease)
- Unknown

<table>
<thead>
<tr>
<th></th>
<th>CCLG</th>
<th>GPOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>59 (39)</td>
<td>63 (19)</td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>53 (35)</td>
<td>55 (17)</td>
</tr>
<tr>
<td>Radiotherapy then surgery</td>
<td>5 (3)</td>
<td>147 (45)</td>
</tr>
<tr>
<td>Surgery then radiotherapy</td>
<td>24 (16)</td>
<td>47 (14)</td>
</tr>
<tr>
<td>None (progressive disease)</td>
<td>9 (6)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>14 (4)</td>
</tr>
</tbody>
</table>

Jeremy Whelan
Department of Oncology, University College Hospitals London NHS

https://doi.org/10.1186/s13569-018-0093-y
• Surgery whenever feasible

• Pre-op RT (44.8Gy) if <50% reduction in soft tissue on imaging after 2 cycles.

• Postop RT
  – Intrallesional surgery – 54.4Gy
  – Marginal surgery with poor response (<90% necrosis) – 54.4Gy
  – Marginal surgery with good response – 44.8Gy
  – Wide resection with POOR response – 44.8Gy

• Radical RT if inoperable
Survival is influenced by approaches to local treatment of Ewing sarcoma within an international randomised controlled trial: analysis of EICESS-92

- Conclusions

How would you apply these to your pediatric patients....?
RT planning – special points

• Extremity lesions: Sparing a strip of linear soft tissue
  – Reduce late fibrosis and edema
    • Oblique opposed fields / angled pairs / rotate the limb
    • Adeq immobilisation – casts / moulds

• Extremity lesions near a joint
  • May reduce margin near growth plate
  • Avoid irradiating both epiphyses of a joint (esp. knee)
  • Avoid irradiating joint surface if feasible
RT planning – special points

• Pelvis
  – Avoid full dose irradiation of bladder (C & I in chemo)
  – Testicular shielding / Ovarian transposition

• Vertebral lesions
  – Uniform irradiation of adjacent vertebra
    • Weighted AP II PA or wedged pair technique

• Rib (Askin’s), pushing into cavities - abdomen
  – Use post chemo volume for Phase I also
    • (be careful about the extension into adjacent cavity wall)
  – Treatment of entire pleural cavity - controversial
Metastatic disease - Lung

• Low dose irradiation beneficial in controlling lung micromets
  – From IESS-I study (VAC+WLI)

• Dose of 12 – 21 Gy
  – 12 Gy / 10#
  – 15 Gy / 10# or 18 Gy / 12#
<table>
<thead>
<tr>
<th>Group/Institution</th>
<th>Primary author</th>
<th>Patient with lung metastasis - Whole lung irradiation</th>
<th>Lung metastasis treatment arms</th>
<th>Type of study</th>
<th>Event free survival</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td>Euro Ewing 99</td>
<td>Haeusler et al.</td>
<td>120</td>
<td>Metastatectomy</td>
<td>Retrospective</td>
<td>25% (3 years)</td>
<td>Not reported</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Metastatectomy + WLI</td>
<td></td>
<td>47%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>WLI alone</td>
<td></td>
<td>23% (3 years)</td>
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<tr>
<td></td>
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<td>none</td>
<td></td>
<td>13% (3 years)</td>
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<tr>
<td>EICESS 92</td>
<td>Bolling T et al.</td>
<td>70/99</td>
<td>WLI (12-21 Gy)</td>
<td>Retrospective</td>
<td>NR</td>
<td>61% (5 years)</td>
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<td></td>
<td></td>
<td>19/99</td>
<td>No WLI</td>
<td></td>
<td></td>
<td>49% (5 years)</td>
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<td>Intergroup sarcoma study</td>
<td>Cangir A et al.</td>
<td>53(I) and 69(II)</td>
<td>WLI (12-20 Gy)</td>
<td>Retrospective</td>
<td>30% (3 years)</td>
<td>30% (5 years)</td>
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<td>5.5-30 Gy</td>
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<td>30% (5 years)</td>
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<td>SFMC</td>
<td>Margolis et al.</td>
<td>7</td>
<td>WLI (12-20 Gy)</td>
<td>Retrospective</td>
<td>NR</td>
<td>28% (3 years)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>20 Gy/10 fr</td>
<td></td>
<td></td>
<td>100% (2 years)</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Rosen et al.</td>
<td>2/12</td>
<td>12-21 Gy</td>
<td>Retrospective</td>
<td>NR</td>
<td>30% (3 years)</td>
</tr>
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<td></td>
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<tr>
<td>CESS</td>
<td>Dunst et al.</td>
<td>22/30</td>
<td>Metastatectomy + WLI</td>
<td>Retrospective</td>
<td>30% (10 years)</td>
<td>44% (10 years)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>WLI (12-20 Gy)</td>
<td></td>
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<tr>
<td>CESS 81,86</td>
<td>Paulussen M et al.</td>
<td>27</td>
<td></td>
<td>Retrospective</td>
<td>36% (5 years)</td>
<td>NR</td>
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<tr>
<td></td>
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<td></td>
<td>WLI (15-18 Gy)</td>
<td></td>
<td>30% (10 years)</td>
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<tr>
<td>St Judes</td>
<td>Spunt S et al.</td>
<td>8/28</td>
<td>16.5 Gy</td>
<td>Retrospective</td>
<td>22.5% (5 years)</td>
<td>37.3% (5 years)</td>
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<tr>
<td></td>
<td></td>
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<td>WLI (15 Gy)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No WLI</td>
<td></td>
<td>66% control (2 years)</td>
<td>22% (5 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
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<tr>
<td>Houston</td>
<td>Paulino et al.</td>
<td>9/19</td>
<td></td>
<td>Retrospective</td>
<td>EFS 34% (4 years)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>WLI (15-18 Gy)</td>
<td></td>
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</tr>
<tr>
<td>EICESS</td>
<td>Paulussen et al.</td>
<td>57/171</td>
<td>WLI (15-18 Gy)</td>
<td>Retrospective</td>
<td>NR</td>
<td></td>
</tr>
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<td>EFS 34% (4 years)</td>
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<tr>
<td>MSKCC</td>
<td>Casey et al.</td>
<td>26</td>
<td>WLI (12-15 Gy)</td>
<td>Retrospective</td>
<td>40% (3 years)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WLI (15 Gy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian Sarcoma Group</td>
<td>Luksch et al.</td>
<td>57/65</td>
<td>WLI (15 Gy)</td>
<td>Retrospective</td>
<td>48% (3 years)</td>
<td>49% (3 years)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>NR – Not reported</td>
<td></td>
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</tr>
</tbody>
</table>
Impact of Whole Lung Irradiation on Survival Outcome in Patients With Lung Relapsed Ewing Sarcoma

Sergiu Scobioala, MD, * Andreas Ranft, MD, † Heidi Wolters, PhD,*

**Results:** The survival outcome was significantly improved after WLI when analyzing the entire group of pulmonary relapsed patients: 3-year PFS 36% (+WLI) versus 14% (−WLI) ($P = .001$); 3-year OS 47% (+WLI) versus 33% (−WLI) ($P = .007$). The 3-year PFS in patients with complete remission of lung relapse receiving WLI (n = 48) compared with those without WLI (n = 40), was 37% (+WLI) versus 21% (−WLI) ($P = .18$). The site of the primary tumor and the response of pulmonary lesions to Ctx were significant prognostic indicators for survival in patients treated with WLI. No severe pulmonary function disorders or lung toxicities were observed after WLI treatment in both pediatric and adult patients.

**Conclusions:** The WLI does not correlate with improved OS in patients with pulmonary relapsed EwS. However, a marginal trend toward superior PFS and improved local control of pulmonary disease suggests the application of WLI in patients with EwS with isolated lung relapse and second clinical remission. © 2018 Published by Elsevier Inc.
Late effects

  - Sparing of uninvolved epiphyseal plates
- RT doses above 60 Gy - markedly increased rates of soft tissue induration and fibrosis
- High-dose circumferential irradiation of an extremity - edema, fibrosis, and compromised limb function
  - sparing of an adequate strip of tissue.
- Weight-bearing bones are at risk for pathologic fractures. The highest risk is within the first 18 months of RT completion
Late effects

- 2\textsuperscript{nd} malignancy
  - RT induced Osteosarcomas
  - Chemo induced leukemias

- Late effects study group: Secondary sarcomas ~ 22\% at 20 yrs
  - Related to RT dose. Esp if > 60 Gy

- With lower doses of RT & Tailored field, lower risk
  - St Jude, NCI, Univ of Florida: 6.5\% at 20 yrs for sarcoma
    - Median time: 7.6 yrs
  - Italian group: 4.7\% at 20 yrs
  - CESS 81,86: 4.7\% at 15 yrs

- MSKCC (Friedman et al. Ped Blood Can 2017 Nov)
  - SMN at 25 years (15\%)
  - 9\% - MDS/AML
  - 6\% - Solid tumors (one was Ca breast – chest wall not irradiated, other was Ca Lung with 30 Pack year smoking and scapula RT)
Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study

664 survivors
Changes in Health Status Among Aging Survivors of Pediatric Upper and Lower Extremity Sarcoma: A Report From the Childhood Cancer Survivor Study

Results

• In adjusted models, when compared with upper extremity survivors, lower extremity survivors had an increased risk of activity limitations but a lower risk of not completing college.

• Compared with those who did not have surgery, those with limb-sparing (LS) and upper extremity amputations (UEAs) were 1.6 times more likely to report functional impairment, while those with an above-the-knee amputation (AKA) were 1.9 times more likely to report functional impairment.

• Survivors treated with LS were 1.5 times more likely to report activity limitations. Survivors undergoing LS were more likely to report inactivity, incomes <$20,000, unemployment, and no college degree.

• Those with UEAs more likely reported inactivity, unmarried status, and no college degree. Those with AKA more likely reported no college degree.
Survivors of Ewings sarcoma apparently returned to normal life with minor limitations.
Summarising

• Ewings – radio responsive tumor

• Indications
  – Radical 55 Gy – 60 Gy (55.8 Gy) Surgery generally preferred !!
  – Postop
    • R1/R2 resection (55.8 Gy)
    • Poor responder (45 Gy)
    • Pelvis / Bulky / All tissues involved by tumor initially – not removed ??
  – Pre-op
    • Inadequate response (36-45 Gy)
  – Metastatic
    • Radical intent Rx if lung mets – WLRT
    • Palliative RT
Thankyou
Case scenario 1

• 11yr old girl
  – Pain Rt lowerlimb – 3m duration
  – Swelling Rt lower back – 1wk
  – No other symptoms
  – Evaluated at nearby hospital
    • MRI – s/o mass lesion
    • Underwent open biopsy (had torrential bleed)
    • s/o – Possibly Ewings  → referred
• Examination
  – Alert & Cooperative child, no dysmorphic features/NC markers
  – General examination, systems – unremarkable
  – Unable to walk due to pain
  – Suture marks of biopsy – Rt lower lumbar region (5-6cm long)
  – Diffuse swelling, mild tenderness
  – No neurological deficits

• Biopsy review – compatible with Ewings/PNET
- **Blood investigations**
  - LDH: 204 U/L
  - Ca : 9.8mg/dL

- **CT chest**: No evidence of mets

- **Bone scan**: uptake at primary site only

- **Bone marrow biopsy**: No evidence of BM infiltration

- **Bone marrow biopsy**: No evidence of BM infiltration

- **Cardiac consult**: ECHO – Normal LVEF
CT chest --- what is defined as lung mets?

- **Definite**
  - 1 nodule > 1cm
  - >1 nodule > 0.5cm

- **Questionable**
  - 1 nodule > 0.5-1cm
  - >1 nodule > 0.3-0.5cm

Suggest Biopsy

EURO EWING 99/2008, COG AEWS0031 Protocols
• Role of PET-CT in replacing Bone marrow biopsy and bone scan, and CT chest?
Case 1 - MRI

- Expansile destructive lesion – posterior aspect of Rt Iliac bone 9x5x8cm
- Cortical break, and soft tissue component infiltrating gluteus medius and minimus, and ilacus muscles, with adjacent soft tissue edema.
- Involvement of Iliac sub-articular margin of Rt SI joint.
- Marrow edema of Rt Sacral Ala
• Tumor volume?

\[ TV = a \times b \times c \times F, \]

where \( a, b, \) and \( c \) represent the maximum tumor dimensions in three planes,

with \( F = \pi / 6 = 0.52 \) for spherical tumors,

or \( F = \pi / 4 = 0.785 \) for cylindrical tumors

282cc
• **Treatment outline**
  a) Chemo → Surgery → Chemo
  b) Chemo → Surgery → PORT → Chemo
  c) Chemo → RT → Surgery → Chemo
  d) Chemo → RT → Chemo
  e) Others?
• Chemo regimen
  a) VDC
  b) VDC/IE q3w
  c) VDC/IE q2w (interval compressed)
  d) VIDE → VAC/VAI
  e) VIDE → Bu-Mel/VAI
• Interval compression
Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children’s Oncology Group

Richard B. Womer, Daniel C. West, Mark D. Krailo, Paul S. Dickman, Bruce R. Pawel, Holcombe E. Grier, ...
HD Chemo, SC support
EURO EWING 99,2008

VIDE
Vincristine 1.5mg/m² D1
Ifosfamide 3g/m² D1-3
Doxorubicin 20mg/m² D1-3
Etoposide 150mg/m² D1-3

VAI
Vincristine 1.5mg/m² D1
Actinomycin D 0.75mg/m² D1-2
Ifosfamide 3g/m² D1-2

Poor histological response ≥ 10% residual viable cells
- Surgery after induction chemotherapy alone

Large tumour ≥200ml
- Surgery after chemo and early radiation therapy
- Initial surgery
- Late radiation therapy

BuMel
Busulfan 16mg/kg over 4 days
Melphalan 140 mg/m² D5

Jeremy Whelan, Marie-Cécile Le Deley, Uta Dirksen, Gwénaël Le Teuff, Bernadette Brennan, Nathalie Gaspar,

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Radiation Dose (Gy)</th>
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</thead>
<tbody>
<tr>
<td>Intralional surgery</td>
<td>54.4</td>
</tr>
<tr>
<td>Marginal surgery with poor histological response ($\geq 10%$ residual tumour cells)</td>
<td>54.4</td>
</tr>
<tr>
<td>Marginal surgery with good histological response ($&lt; 10%$ residual tumour cells)</td>
<td>44.8</td>
</tr>
<tr>
<td>Wide resection with poor histological response ($\geq 10%$ residual tumour cells)</td>
<td>44.8</td>
</tr>
</tbody>
</table>
MRI – Post chemo

- Rt iliac bone lesion, involving articular surface of sacrum.
  - 8x4.5x8cm.
- No infiltration to sacrum, Acetabulum appears normal.
- Intra and extra pelvis soft tissue abutting iliacus and gluteal muscle, no obvious infiltration.
- Fat plane with vessels maintained.
Local control modality

a) Surgery
b) Radiotherapy
c) Surgery + RT
d) RT+ Surgery
Surgery

– Would it be possible to perform a wide excision with adequate margins?
  • If No, how to proceed
    – GO ahead with surgery?
    – RT and then surgery?
    – Radical RT?

– What structures need to be excised?
  • Only residual disease – soft tissue component, involved bone?
  • Previously involved muscles also?

– Is PORT anticipated?

– What would be the expected morbidity?
  • Immediate
  • Long term
Would it be possible to perform a wide excision with adequate margins?

- If No, how to proceed
  - GO ahead with surgery?
  - RT and then surgery?
  - Radical RT?

No benefit of intra-lesional excision+ post-op RT vs. Radical RT
tumors. Low-dose (36.0 Gy) preoperative RT was encouraged on AEWS1031 as a method to improve local tumor control for large pelvis tumors. The results of this study are still pending.

AEWS1031

undertaken whenever possible. Preoperative radiotherapy (44.8 Gy) was recommended when there was < 50% reduction of a soft tissue component, evident on repeat imaging after 2 chemotherapy courses. Radiotherapy

EURO EWING99
-Whelan etal, Clin Sarcoma Res 2018

imaging after 2 chemotherapy courses. Radiotherapy (54.4 Gy) replaced surgery for tumours deemed inoperable. Post-operative radiotherapy (54.4 Gy) was recommended after intralesional surgery or marginal surgery with poor response (< 90% necrosis). Postoperative
• Subsites of pelvis
  – Surgery – Morbid
  – Surgery – Less morbid
Surgery

– Would it be possible to perform a wide excision with adequate margins?
  • If No, how to proceed
    – GO ahead with surgery?
    – RT and then surgery?
    – Radical RT?

– What structures need to be excised?
  • Only residual disease – soft tissue component, involved bone?
  • Previously involved muscles also?

– Is PORT anticipated?

– What would be the expected morbidity?
  • Immediate
  • Long term
Assessing Margins of Resection

• What is considered adequate margin?
  – Bone margin
  – Soft tissue Margin
• Bone margin: 2 to 5 cm
  – 1 cm may be adequate
• Fat, muscle, and medullary bone: 5 mm
• Fascia, periosteum and intermuscular septa: 2 mm
Assessing response to chemotherapy
Pathological response assessment

• What method do you use?
  – Huvos or modified Huvos
  – CCG / POG grading scheme
  – Salzer-Kuntschik
### HUVOS grading scheme

<table>
<thead>
<tr>
<th>Necrosis</th>
<th>Grade</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>No necrosis</td>
<td>I</td>
<td>No Rx effect</td>
</tr>
<tr>
<td>&lt;50% necrosis</td>
<td>IIA</td>
<td>Partial/Low</td>
</tr>
<tr>
<td>50-95% necrosis</td>
<td>IIB</td>
<td>Partial/high</td>
</tr>
<tr>
<td>96-99% necrosis</td>
<td>III</td>
<td>Scattered viable foci</td>
</tr>
<tr>
<td>100% necrosis</td>
<td>IV</td>
<td>No viable tissue</td>
</tr>
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</table>

### CCG / POG grading scheme

<table>
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<tr>
<th>Necrosis</th>
<th>Grade</th>
<th>3yr survival</th>
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</thead>
<tbody>
<tr>
<td>No chemo effect</td>
<td>I</td>
<td>30%</td>
</tr>
<tr>
<td>1-10% necrosis</td>
<td>IIA</td>
<td>30%</td>
</tr>
<tr>
<td>11-90% necrosis</td>
<td>IIB</td>
<td>49%</td>
</tr>
<tr>
<td>91-99% necrosis</td>
<td>III</td>
<td>73%</td>
</tr>
<tr>
<td>100% necrosis</td>
<td>IV</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Any issues in assessing tumor response for Ewing??**

Ref: Protocol for the Examination of Specimens From Patients With Primitive Neuroectodermal Tumor (PNET)/Ewing Sarcoma (ES) © 2012 College of American Pathologists (CAP).
## Histologic Response

<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&lt;br&gt; &gt;10% viable tumor cells</td>
<td>64%</td>
<td>38%</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>59%</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>≤95% necrosis&lt;br&gt; &gt;95% necrosis</td>
<td>36%</td>
<td>44%</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

Slide courtesy: Ahmed S, Mayo Clinic 2017
Radiological response assessment

- MRI
  - Is soft tissue response assessment sufficient?

Prognostic Factors and Patterns of Relapse in Ewing Sarcoma Patients Treated With Chemotherapy and R0 Resection

**CONCLUSIONS**—Histologic and radiologic response to chemotherapy were independent predictors of outcome. Additional study is needed to determine the role of adjuvant RT for patients who have poor histologic response after R0 resection.

-Pan, Mahajan, IJROBP 2015 June.
Radiologic Response

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

Andreu et al., CTOS Annual Meeting, 2016
Gaspar et al., Eur J Cancer, 2012
SUV at diagnosis was significantly lower in patients with good histological response than in patients with poor histological response. The positive predictive value of an SUV II ≤ 2.5 for favorable response was 84.21%, and the median SUV II was significantly higher in patients with disease progression (2.3 vs. 1.6, p = 0.04).
Adjuvant treatment

• Chemotherapy
  – Role for chemo intensification?
  – Role of HD chemo with SC support?
• **Adjuvant radiation**
  - Margin positive
    • Microscopic +ve
    • Gross residual
  - Inadequate margin / close margin ?
  - Margin negative ?
    • In poor responder ?
  - Size >8cm ?
  - Volume >200ml ?
• Adjuvant radiation
  – Role in complete pathological response?

**Results:** One hundred forty-two (24%) of the 599 patients included from 1999 to 2009 received PORT (median dose: 45 Grays). With median follow-up of 6.2 years, 67 patients had an LR (with concomitant metastases in 28), leading to an 8-year LR-incidence = 11.9% (standard error [se] = 1.4%). Overall survival (OS) = 21% (se = 5%) 3 years after LR (31% in isolated LR). Controlling for possible confounders, we observed a statistically significant reduction of LR in patients treated by surgery + PORT compared to surgery alone (subdistribution-hazard ratio = 0.45, 95% confidence interval 0.21–0.88, p = 0.02). The benefit of PORT was particularly marked for tumours larger than 200 ml at diagnosis and 100% necrosis. We observed a non-significant trend for benefit associated with PORT for disease-free, event-free and OS.

**Conclusion:** Radiotherapy appears to improve local control. We now recommend PORT in case of incomplete removal of the tissues involved by the pre-chemotherapy tumour volume. Further studies are required to assess the balance between benefit and risks.
<table>
<thead>
<tr>
<th>Description</th>
<th>PORT vs no PORT</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>3/18 vs 8/83</td>
<td>0.31</td>
</tr>
<tr>
<td>Other countries</td>
<td>10/124 vs 46/374</td>
<td></td>
</tr>
<tr>
<td>&lt; 14 years</td>
<td>7/60 vs 21/234</td>
<td>0.15</td>
</tr>
<tr>
<td>≥ 14 years</td>
<td>6/82 vs 33/223</td>
<td></td>
</tr>
<tr>
<td>Osseous lesion +/- soft</td>
<td>12/123 vs 48/416</td>
<td>0.57</td>
</tr>
<tr>
<td>Soft tissue only</td>
<td>1/19 vs 6/41</td>
<td></td>
</tr>
<tr>
<td>Limb</td>
<td>6/47 vs 18/277</td>
<td>0.07</td>
</tr>
<tr>
<td>Sacrum or vertebrae</td>
<td>1/16 vs 4/11</td>
<td>0.015*</td>
</tr>
<tr>
<td>Pelvis other than sacrum</td>
<td>1/23 vs 13/57</td>
<td></td>
</tr>
<tr>
<td>Other axial site</td>
<td>5/56 vs 19/112</td>
<td></td>
</tr>
<tr>
<td>&lt; 200 mL</td>
<td>6/67 vs 26/309</td>
<td>0.35</td>
</tr>
<tr>
<td>≥ 200 mL</td>
<td>7/75 vs 28/148</td>
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<tr>
<td>Complete resection</td>
<td>7/81 vs 46/426</td>
<td>0.48</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>6/61 vs 8/31</td>
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</tr>
<tr>
<td>Complete necrosis</td>
<td>1/65 vs 35/299</td>
<td>0.001</td>
</tr>
<tr>
<td>Incomplete necrosis</td>
<td>12/77 vs 19/158</td>
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<tr>
<td>Overall</td>
<td>13/142 vs 54/457</td>
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</table>

subHR\textsubscript{(PORT)} = 0.43 (95%CI, 0.21-0.88) 

p = 0.02
## PORT – RT Dose

<table>
<thead>
<tr>
<th>Margin negative</th>
<th>Poor response</th>
<th>Bulky disease, good response</th>
<th>Bulky disease, poor response</th>
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<tbody>
<tr>
<td>R1 resection</td>
<td>Good response</td>
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<tr>
<td></td>
<td>Poor response</td>
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<tr>
<td>R2 resection</td>
<td>Good response</td>
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<tr>
<td></td>
<td>Poor response</td>
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</table>

### European

<table>
<thead>
<tr>
<th>Surg .margins</th>
<th>Necrosis 100 %</th>
<th>Necrosis &lt;100 %</th>
<th>Boost</th>
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<tbody>
<tr>
<td>Negative</td>
<td>NO RT</td>
<td>45 Gy</td>
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<tr>
<td>Close (&lt; 1cm)</td>
<td>45 Gy</td>
<td>50 Gy</td>
<td>5.4 Gy</td>
</tr>
<tr>
<td>Micro R1</td>
<td>45 Gy</td>
<td>50 Gy</td>
<td>5.4 Gy</td>
</tr>
<tr>
<td>Gross R2</td>
<td>50 Gy</td>
<td>55 Gy</td>
<td>5.4-10-8</td>
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<tr>
<td>Indications</td>
<td>Gross or microscopic positive margins</td>
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<td>------------------------------------------------------</td>
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<tr>
<td></td>
<td>Clear margins but poor histopathological response to chemotherapy (necrosis &lt;90% is the suggested minimum threshold, but &lt;95–99% may be used based on institutional practice)</td>
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<tr>
<td>Timing</td>
<td>Within 6–8 weeks of surgery (though there is no evidence to suggest that a further delay leads to inferior outcomes)</td>
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<tr>
<td>Dose</td>
<td>45 Gy to the pre-chemotherapy volume</td>
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<tr>
<td></td>
<td>10.8 Gy boost to areas of gross tumor residual</td>
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<tr>
<td>Fractionation</td>
<td>Standard daily fractionation of 1.8 Gy per fraction</td>
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<td></td>
<td>Hyperfractionated RT (with equivalent total dose) may be used to reduce long term side effects</td>
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<tr>
<td>Target volume</td>
<td>Initial phase (45 Gy): pre-chemotherapy tumor volume on MRI with 1.5–2 cm margins. Appropriate modifications should be made in tumors expanding into cavities or the lung</td>
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<tr>
<td></td>
<td>Boost phase (10.8 Gy): post-operative gross residual disease with 1.5–2 cm margins</td>
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<td></td>
</tr>
</tbody>
</table>

*Laskar S. Pediatr Blood Cancer 2008;51:575–580*
**Definitely PORT**
Positive margin/Gross
Poor responder

**Definitely No RT**
Limb tumor < 200ml
Clear surgical margins
Complete necrosis

**??**
Pelvis subsite
Bulk, >200ml
Incomplete removal of involved soft tissue
Radical Radiotherapy

• Volume irradiated
  – GTV
  – CTV
  – Boost (higher dose) volume:
EURO EWING99
Axial
GTV: Pretreatment extent
Safety margin: 2cm margin all around

Extremity
GTV: Pretreatment extent
Safety margin: 3-5cm proximal&distal
and 2cm other directions
Boost volume
2cm proximal&distal, 1-2cm other directions

GTV1: Pretreatment tumor
CTV1+PTV1: 2-2.5cm margin

GTV2: Postchemo volume
CTV2+PTV2: 1.5-2cm margin


AEWS1031
GTV: Prechemo bony disease and
Post chemo soft tissue
CTV: Margin of 1-1.5cm (covering
biopsy site/drain site)

AEWS slide courtesy: Nima Nabavizadeh

Modifications around cavities?
Radical Radiotherapy

- Dose:

- Dose escalation?
• Dose escalation studies
  – Patients treated with definitive radiation doses ≥5,600 cGy had a lower incidence of local recurrence (17% vs. 28%, \( P = 0.61 \)).
      » Anatomical localisation correlated with outcome
      » Local control poorer with radical RT
      » Sx+RT and Definitive RT with dose ≥ 56Gy – better LC
• Morbidity expected
  – Muscle / Soft tissue / Bone
  – Fertility
  – Bladder / bowel
  – 2\textsuperscript{nd} Malignancy
Long term morbidity
Up to 25 years after 5-year survival, bone sarcoma survivors are at substantial risk of death and SPNs, but this is greatly reduced thereafter.
Sx vs. Sx+RT vs. RT

• Best oncological results?

• Best functional results?
• Sx vs. RT vs. Combination
Prognostic factors

- Metastatic disease vs Non metastasis
  - Metastatic : Non Pulmonary vs Pulmonary

- Site
  - Pelvic (central) vs Extremity

- Bulk
  - >8cm, >200ml

- Response to chemo
  - <90% (<95%) vs >90% necrosis
  - Radiological response
  - ?PET response

- Age
Case 2
• 5yr old boy
  – Fever, cough, dyspnoea of <1wk duration.
  – CXR s/o ? Massive effusion Left chest

  – CT Thorax: Large solid cystic heterogenously enhancing mass entire left hemithorax
    • 12x10x16cm
    • Lung parenchyma compressed medially
    • Mediastinal shift +
- Trucut biopsy and ICD insertion was done by Pediatric surgeon.
- ICD drained hemorrhagic fluid
  - Cytology: negative, cell block preparation – not done.

- Biopsy: Small round cell tumor – IHC s/o Ewings
- Bone scan: Lytic sclerotic lesion left 5th rib lateral 1/3rd
- BM biopsy: Normal
• Started on chemotherapy with VDC-IE
• Surgery
  – Chestwall resection with bone cement mesh reconstruction and LD flap cover
    • Epicenter located in the lateral portions of 4,5,6\textsuperscript{th} ribs
    • Adherent to surface of the lung
    • No pleural nodules
    • Lesion excised with portion of adherent lung

• HPR: Sections from chest wall and lung shows chronic inflammation. No residual malignancy identified.
• Role of adjuvant RT?

• Role of RT for pleural effusion?
  – Hemithorax RT?
    • Timing?
    • Dose?
  – What if primary also requires RT?
Chestwall Ewing – PORT?

### Local Control in Ewing Sarcoma of the Chest Wall: Results of the EURO-EWING 99 Trial

- **Multivariate analysis – EFS**
  - Large volume (>200ml)
  - Poor response to chemo

198 patients
- Sx 85 (43%)
- PORT 106 (53%)
- RT 7 (4%)

Conclusions. Complete tumor resection is the best way to achieve local control of ES of the chest wall; additional RT is only useful in patients with incomplete resection. The main limitation of this study was its retrospective nature.

How much of rib to excise?
- Whole rib / partial ??
- Adjacent ribs also ?? (Sabanathan et al. and Saenz et al.)
A combination of neoadjuvant chemotherapy followed by surgery and radiotherapy resulted in optimal outcome in patients with this rare tumor.
Summary

• Local control an important component of multimodality treatment of Ewings

• Choice of local treatment highly individualised

• Local failure rates higher with conventional dose radical radiotherapy
Summary

• Surgery + PORT to be considered when feasible.

• Take into consideration
  – Best oncological outcome
  – Best functional outcome
  – Late morbidity

Thank You
<table>
<thead>
<tr>
<th>Week</th>
<th>Regimen A1, Surgery only</th>
<th>Regimen A2, Radiation only</th>
<th>Regimen A3, Surgery then Radiation</th>
<th>Regimen B1, Surgery only</th>
<th>Regimen B2, Radiation only</th>
<th>Regimen B3, Surgery then Radiation</th>
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<td>Cycle 5 (VDC) start RT</td>
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</table>

IE = Ifosfamide – Etoposide – MESNA
VDC = Vincristine – Doxorubicin – Cyclophosphamide – MESNA
VC = Vincristine – Cyclophosphamide – MESNA
• VDC
  – Vincristine 2mg/m² (max 2mg) D1
  – Doxorubicin 37.5mg/m² D1,D2 (cumulative 375mg)
  – Cyclophosphamide 1.2gm/m² D1

• IE
  – Ifosfamide 1.8gm/m² D1-D5
  – Etoposide 100 mg/m² D1-D5
Candidates for radiotherapy alone will include patients with bulky lesions in surgically difficult sites such as the spine, skull and periacetabular pelvis, and those patients with a poor response to induction chemotherapy, in whom surgery would result in unacceptable functional results. Sites which if removed would result in significant impairment of function include: skull, facial bones, vertebrae and pelvic bones about the acetabulum. In some cases, resection even in these sites may be feasible in combination with radiation therapy, and decisions regarding a specific patient must be individualized.

**Surgery + RT**

risk in each patient. This approach is most appropriate for large bulky primaries, greater than 10 cm. in maximal dimension, or when the lesion is unresectable after induction chemotherapy. The use of routine postoperative radiotherapy will permit use of a more limited surgical procedure, and will be administered in any patient who has residual disease, or inadequate surgical margins. The decision regarding whether the radiation will precede or follow the resection will be left to the treating team. This should be planned in advance with the pediatric oncologist and the radiation oncologist. When surgery is done first, followed by radiation therapy, surgery should occur on week 13 (after 4 cycles of chemotherapy on Regimen A or 6 cycles of chemotherapy on Regimen B (see Section 5.1). Radiation therapy should begin as soon as feasible thereafter.
Euro-Ewing’s 2012 trial schema

**Randomisation 1**

**ARM A**
VIDE strategy

**Induction Chemotherapy**

**ARM B**
VDC/IE strategy

**Consolidation Chemotherapy**

**Randomisation 2**

**Localised Disease**
- Good Risk
  - R2 VAC
  - + Zoledronic acid
  - - Zoledronic acid

**Localised Disease**
- Poor Risk or Pulmonary/Pleural Metastatic Disease
  - R2 VAI
  - + Zoledronic acid
  - - Zoledronic acid

**Localised Disease**
- or Pulmonary/Pleural Metastatic Disease
  - R2 IEVC
  - + Zoledronic acid
  - - Zoledronic acid

**Chemotherapy regimens**

**VIDE**
- Vincristine, Ifosfamide, Doxorubicin, Etoposide

**VDC**
- Vincristine, Doxorubicin, Cyclophosphamide

**IE**
- Ifosfamide, Etoposide

**VAI**
- Vincristine, Actinomycin D, Ifosfamide

**VAC**
- Vincristine, Actinomycin D, Cyclophosphamide

**IE**
- Ifosfamide, Etoposide

**VC**
- Vincristine, Cyclophosphamide

(Pulmonary/pleural mets only)
- + Lung radiotherapy