EWINGS SARCOMA
JAMES EWING, 1921

Endothelial origin

14 yr Girl
SPECTRUM OF ESFT

NEURAL DIFFERENTIATION

Least ➔ Well

EWING’S SARCOMA

ATYPICAL EWING’S SARCOMA

• PNET
• Peripheral Neuroepithelioma
• ASKIN TUMOR (thoraco-pulmonary)
GENETICS

- Most Consistent: Pathognomic of EFT

- 85%: Reciprocal Translocation \( t(11;22) \) (q24;q12)

- Results EWS-FLI1 gene

- 5-10%: Translocation \( t(21;22)(q21;q12) \)

- Results EWS-ERG gene
Epidemiology

- 2nd most common primary osseous malignancy in children
- Incidence is 2.1 / million (U.S.)
- Males > Females
- 65% in the 2nd decade of life
- Rare in blacks and Asians
Age distribution of Ewing’s sarcoma patients registered with CESS and UKCCSG/MRC

Median age -14 years

Age in years at diagnosis

Number of patients

n = 975

S.J. Cotterill et al, JCO: 18;2000, 3108-3114
CLINICAL PRESENTATION

- Pain 90%
- Swelling 80%
- Impaired limb movement 25%
- Neurological symptoms 10%
- Fever 5%
- Symptoms of metastatic disease
SITES OF INVOLVEMENT

- Skull (3.8%)
- Scapula (3.8%)
- Humerus (4.8%)
- Pelvis (24.7%)
- Hand (1.2%)
- Femur (16.4%)
- Tibia (7.6%)
- Clavicle (1.2%)
- Ribs (12.1%)
- Spine (8.0%)
- Radius (1.9%)
- Other bones (0.7%)
- Fibula (6.7%)
- Foot (2.4%)

S.J. Cotterill et al, JCO: 18;2000, 3108-3114
INVESTIGATIONS

Pathology
   Biopsy with routine histology
   Immunohistochemistry
   Cytogenetics

Laboratory
   Routine chemistries, LDH

Radiography
   X Ray of the primary
   CT Scan & MRI of the primary
   Chest CT Scan
   Bone scan
   PET-CT Scan

Bone marrow aspirate and biopsy
BIOPSY

- Multiple core
- Open Inx biopsy Longitudinal
- Soft tissue extension

Tissue Processing

- Cytogenetics (Karyotyping)
- Molecular RT-PCR & Immuno-cytochemical studies
- Flow Cytometry – DNA ploidy
IMMUNOHISTOCHEMISTRY

- **Ewing’s sarcomas**
  - MIC2 positive
  - PAS-positive
  - Reticulin negative

- **Lymphomas**
  - PAS-negative and Reticulin-positive
  - Positive for leukocyte common antigen and other T and B cell markers

- **Embryonal Rhabdomyosarcoma**
  - Positive for Desmin, myoglobin and muscle-specific actins.

- **Small-cell metastatic carcinomas & Melanomas**
  - Express detectable Cytokeratin.

- **Primitive Neuroectodermal Tumors (PNET)**
  - Neural differentiation by light microscopy (Homer Wright rosettes in more than 20% of tumor tissue) and immunohistochemical staining for neuron-specific enolase (NSE), S-100, Leu-7
X-RAY

Periosteal Lamellation (circular)

Diaphyseal Tumour

Soft Tissue Component

S Laskar ICRO July 2015
MRI

- Intraossous extension
- Soft tissue extension
- Skip lesions
- Relation to adjacent structures, vessels, nerves
- Intra-medullary extent
- Multi-planar reconstruction
PROGNOSTIC FACTORS

- Site
- Stage: localised / metastatic
- Size
- Age
- Molecular prognostic factors
- Response to chemotherapy (Necrosis)
- Minimal residual disease
RFS by primary site for patients free of metastases at diagnosis.

S.J. Cotterill et al, JCO: 18;2000, 3108-3114
Table 3. RFS by Primary Site in Patients Without Metastases at Diagnosis

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients</th>
<th>5-Year RFS (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axial sites</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>179</td>
<td>46</td>
<td>38-54</td>
</tr>
<tr>
<td>Rib</td>
<td>97</td>
<td>53</td>
<td>42-63</td>
</tr>
<tr>
<td>Spine</td>
<td>58</td>
<td>58</td>
<td>45-72</td>
</tr>
<tr>
<td>Scapula</td>
<td>38</td>
<td>41</td>
<td>25-56</td>
</tr>
<tr>
<td>Skull</td>
<td>20</td>
<td>68</td>
<td>43-93</td>
</tr>
<tr>
<td>Clavicle</td>
<td>14</td>
<td>32</td>
<td>4-61</td>
</tr>
<tr>
<td>Sternum</td>
<td>2</td>
<td>50*</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>408</td>
<td>40</td>
<td>31-51</td>
</tr>
<tr>
<td><strong>Extremities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>139</td>
<td>58</td>
<td>49-66</td>
</tr>
<tr>
<td>Humerus</td>
<td>49</td>
<td>78</td>
<td>66-90</td>
</tr>
<tr>
<td>Tibia</td>
<td>82</td>
<td>63</td>
<td>52-74</td>
</tr>
<tr>
<td>Fibula</td>
<td>78</td>
<td>55</td>
<td>44-67</td>
</tr>
<tr>
<td>Foot</td>
<td>24</td>
<td>51</td>
<td>29-72</td>
</tr>
<tr>
<td>Ulna</td>
<td>7</td>
<td>71*</td>
<td>-</td>
</tr>
<tr>
<td>Radius</td>
<td>7</td>
<td>86*</td>
<td>-</td>
</tr>
<tr>
<td>Hand</td>
<td>2</td>
<td>100*</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>388</td>
<td>61</td>
<td>56-66</td>
</tr>
<tr>
<td><strong>All sites combined</strong></td>
<td></td>
<td>56</td>
<td>52-59</td>
</tr>
</tbody>
</table>

S.J. Cotterill et al, JCO: 18;2000, 3108-3114
LOCALISED VS. METASTATIC

RFS according to detectable metastases at diagnosis.

Met. free (n=796)

Metastases (n=179)

p < 0.0001

55 %

21 %

S.J. Cotterill et al, JCO: 18;2000, 3108-3114

S Laskar ICRO July 2015
SITES OF METASTASIS

Survival by site of metastases (figure excludes 1 patient for whom site of metastasis was not specified).

S.J. Cotterill et al, JCO: 18;2000, 3108-3114
## RESPONSE TO CHEMOTHERAPY

### Huvos Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Necrosis (%)</th>
<th>5 yr EFS %</th>
<th>Responders %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;50</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>II</td>
<td>50-90</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>III</td>
<td>90-99</td>
<td>84</td>
<td>18</td>
</tr>
<tr>
<td>IV</td>
<td>100</td>
<td>84</td>
<td>42</td>
</tr>
</tbody>
</table>

### POG-CCG (Modified Huvos System)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Necrosis (%)</th>
<th>OS – 3 yrs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>II</td>
<td>A – 1 to 10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>B – 11 to 90</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>91-99</td>
<td>49</td>
</tr>
<tr>
<td>IV</td>
<td>100</td>
<td>73</td>
</tr>
</tbody>
</table>

S Laskar ICRO July 2015
TREATMENT

- Multi-disciplinary treatment
- Current standard treatment
  - Primary induction chemotherapy
  - Local therapy (Surgery / radiotherapy)
  - Maintenance chemotherapy
CHEMOTHERAPY

1960 – Sutow & Pinkel: Cyclophosphamide 3/4 response


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


1976 – Rosen MSKCC: RT + VACD Long term survival

1990 – Nesbitt: VACD vs. VAC – Improved EFS & LC
## Treatment results in selected clinical studies of localized Ewing’s sarcoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Schedule</th>
<th>Patients</th>
<th>5-year EFS</th>
<th>p value*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IESS studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VAC + WLI</td>
<td></td>
<td>44%</td>
<td></td>
<td>Benefit of WLI?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VACD</td>
<td></td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IESS-II (1978–1982)</td>
<td>Burgert et al. [69]</td>
<td>VACD-HD</td>
<td>214</td>
<td>68%</td>
<td>.03</td>
<td>Value of aggressive cytoreduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VACD-MD</td>
<td></td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First POG–CCG, INT-0091</td>
<td>Grier et al. [75]</td>
<td>VACD</td>
<td>200</td>
<td>54%</td>
<td>.005</td>
<td>Value of combination IE in localized disease, no benefit in metastatic disease</td>
</tr>
<tr>
<td>(1988–1993)</td>
<td></td>
<td>VACD + IE</td>
<td>198</td>
<td>69%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second POG–CCG (1995–1998)</td>
<td>Granowetter et al. [98]</td>
<td>VCD + IE48 weeks</td>
<td>492</td>
<td>75% (3 yrs)</td>
<td>.57</td>
<td>No benefit of dose-time compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VCD + IE30</td>
<td></td>
<td>76% (3 yrs)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Paulussen et al. The Oncologist 2006;11:503–519*
<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Schedule</th>
<th>Patients</th>
<th>5-year EFS</th>
<th>p value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CESS studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CESS-81</td>
<td>Jürgens et al.</td>
<td>VACD</td>
<td>93</td>
<td>&lt;100 ml, 80%; ≥100 ml 31% (both 3 yrs)</td>
<td></td>
<td>Tumor volume (&lt; or ≥100 ml) and histological response are prognostic factors</td>
</tr>
<tr>
<td>(1981–1985)</td>
<td>[67]</td>
<td></td>
<td></td>
<td>Viable tumor &lt;10%, 79%; &gt;10%, 31% (both 3 yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CESS-86</td>
<td>Paulussen et al.</td>
<td>&lt;100 ml (SR): VACD</td>
<td>301</td>
<td>52% (10 yrs)</td>
<td></td>
<td>Intensive treatment with I for high-risk patients. Tumor volume (&lt; or ≥200 ml) and histologic response as prognostic factor</td>
</tr>
<tr>
<td>(1986–1991)</td>
<td>[73]</td>
<td>≥100 ml (HR): VAID</td>
<td></td>
<td>51% (10 yrs)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Paulussen et al. The Oncologist 2006;11:503–519*
COMPARISON OF VACD vs. VACD + IE

Non metastatic (398)

Randomise

200 – standard therapy VACD
198 – experimental therapy VACD alt I+E

Metastatic (120)

Randomise

62 – standard arm
58 – experimental arm

Primary End-point: Event free survival

Without Mets
The 5 year EFS
Exper group - 69 %
Standard - 54 %

With Mets
The 5 year EFS
Exper - 22 ± 5 %
Standard - 22 ± 6 %

Figure 1. Event-free Survival According to Study Group and the Presence or Absence of Metastatic Disease.

RESULTS

- Addition of I+E to VACD improved outcomes in patients with Non-metastatic Ewing’s sarcoma BUT not with Metastatic disease

- Improvement was greatest with large primary tumors or primary tumors of the pelvis
LOCAL THERAPY FOR ESFT: EVOLUTION

- 1970s: limited imaging
  - Most patients received radiation therapy
  - Field encompassed the entire medullary cavity of the bone and all soft tissue extensions
  - Dose: 5500-6500 Gy

- 1980s: Neoadjuvant chemotherapy/ improved imaging
  - Smaller field size: 3 cm margin in current trials
  - Improved technique/better machinery
  - Dose: 4500-6500 Gy
  - New surgical options available
    - Prosthesis
Sx vs. XRT: RETROSPECTIVE REVIEWS

- Patients who undergo primary surgery have a better prognosis than patients who receive XRT
  Selection bias: patients with smaller tumors and better prognostic sites are more likely to have surgery

- Patients who receive surgery/XRT have better prognosis than XRT alone (Sailer, MGH 1988)
  - 92% survival with surgery vs. 37% survival without surgery, significant on univariate analysis
<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>CESS 81, CESS 86, EICESS 92</td>
<td>70/266 (26.3)</td>
<td>13/246 (5.3)</td>
<td>41/546 (7.5)</td>
<td>10/242 (4.1)</td>
<td>31/304 (10.2)</td>
</tr>
<tr>
<td>CESS 86, EICESS 92</td>
<td>50/222 (22.5)</td>
<td>11/239 (4.6)</td>
<td>29/452 (6.4)</td>
<td>5/192 (2.6)</td>
<td>24/260 (9.2)</td>
</tr>
<tr>
<td>Central</td>
<td>44/188 (23.4)</td>
<td>10/118 (8.5)</td>
<td>36/251 (14.3)</td>
<td>6/71 (8.5)</td>
<td>30/180 (16.7)</td>
</tr>
<tr>
<td>Proximal</td>
<td>14/46 (30.4)</td>
<td>0/59 (0)</td>
<td>2/138 (1.4)</td>
<td>1/77 (1.3)</td>
<td>1/61 (1.6)</td>
</tr>
<tr>
<td>Distal</td>
<td>12/32 (37.5)</td>
<td>3/69 (4.3)</td>
<td>3/157 (1.9)</td>
<td>3/94 (3.1)</td>
<td>0/63 (0)</td>
</tr>
<tr>
<td>Tumor volume (cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>17/93 (18.3)</td>
<td>2/85 (2.4)</td>
<td>12/172 (6.9)</td>
<td>5/82 (6.1)</td>
<td>7/90 (7.8)</td>
</tr>
<tr>
<td>≥100</td>
<td>39/137 (28.5)</td>
<td>10/150 (6.7)</td>
<td>21/314 (6.6)</td>
<td>3/133 (2.3)</td>
<td>18/181 (9.9)</td>
</tr>
<tr>
<td>Radical resection</td>
<td>—</td>
<td>0/4 (0)</td>
<td>1/68 (1.4)</td>
<td>1/63 (1.6)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Wide resection</td>
<td>—</td>
<td>8/165 (4.8)</td>
<td>19/318 (5.9)</td>
<td>6/145 (4.1)</td>
<td>13/173 (7.5)</td>
</tr>
<tr>
<td>Marginal resection</td>
<td>—</td>
<td>0/30 (0)</td>
<td>4/70 (5.7)</td>
<td>1/18 (5.6)</td>
<td>3/52 (5.8)</td>
</tr>
<tr>
<td>Intralesional resection</td>
<td>—</td>
<td>1/14 (7.1)</td>
<td>11/51 (21.5)</td>
<td>2/7 (28.6)</td>
<td>9/44 (20.5)</td>
</tr>
<tr>
<td>Good histologic response after initial chemotherapy</td>
<td>—</td>
<td>—</td>
<td>14/282 (4.9)</td>
<td>3/154 (2)</td>
<td>11/128 (8.6)</td>
</tr>
<tr>
<td>Poor histologic response</td>
<td>—</td>
<td>—</td>
<td>11/150 (7.3)</td>
<td>3/46 (6.5)</td>
<td>8/104 (7.7)</td>
</tr>
</tbody>
</table>
### 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><strong>Wide resection and good histologic response</strong></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><strong>Wide resection and poor histologic response</strong></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>
LOCAL THERAPY IN LOCALIZED EWING TUMORS: RESULTS OF 1058 PATIENTS TREATED IN THE CESS 81, CESS 86, AND EICESS 92 TRIALS

Definitive RT: reduced EFS

EFS according to local therapy in CESS 81, CESS 86, and EICESS 92.


S Laskar ICRO July 2015
## LOCAL THERAPY & EFS

<table>
<thead>
<tr>
<th>Study</th>
<th>% 5yr EFS</th>
<th>local therapy in %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>all</td>
<td>Sx</td>
</tr>
<tr>
<td>CESS 81</td>
<td>54 ± 10%</td>
<td>55 ± 18%</td>
</tr>
<tr>
<td>CESS 86</td>
<td>61 ± 7%</td>
<td>62 ± 15%</td>
</tr>
<tr>
<td>EICESS 92</td>
<td>64 ± 6%</td>
<td>72 ± 13%</td>
</tr>
</tbody>
</table>
RADIOTHERAPY - INDICATIONS

Definitive Radiotherapy

Location (Unfavourable): Axial, Pelvic with involvement of adjacent joints

Intralesional resection expected

Post-op adjuvant Radiotherapy

Gross or microscopic positive margin

Poor histological response to chemo

Pre Treatment Fracture/ Hematoma/ Tissue Violation
TARGET VOLUME

Phase I (Large volume) (45Gy/ 25#/ 5wks):
Pre-chemotherapy tumor volume on MRI + 1.5-3 cm longitudinal margin

   Appropriate modifications into cavities or the lung

Phase II (Boost) (10.8Gy/ 6#/ 2wks):

   Post-operative/ Post - CTh gross residual disease + 1.5–2 cm margins
A MULTIDISCIPLINARY STUDY INVESTIGATING RADIOTHERAPY IN EWING’S SARCOMA: END RESULTS OF POG #8346

Sarah S. Donaldson, M.D.,* Margaret Torrey, M.D.,* Michael P. Link, M.D.,* Arvin Glicksman, M.D.,† Louis Gilula, M.D.,‡ Fran Laurie, B.S.,† John Manning, M.D.,§ James Neff, M.D.,‖ William Reinus, M.D.,‡ Elizabeth Thompson, M.D.,* Jonathan J. Shuster, Ph.D.,‖

- 178 eligible patients
- 141 (79%) had localized disease and 37 (21%) had metastatic disease
- 37 of the localized patients underwent resection of whom 16 (43%) required postoperative radiotherapy
- Remaining 104 localized patients were eligible for randomization to receive radiotherapy
94 patients received radiotherapy.

Forty patients were randomized to receive either Whole bone (n = 20) vs. Involved field (n = 20) RT.

Outcome by treatment field:

- 5-year EFS:
  - Whole bone: 37%
  - Involved Field: 39%

Conclusion: Tailored Portals for Radiotherapy in Ewing’s Sarcoma
## POST-OP ADJUVANT RADIOTHERAPY

<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>
TIMING OF POST-OPERATIVE RADIATION

In an analysis of patients receiving PORT in the CESS 86 and EICESS trials,

**Schuck et al**
No significant difference in the local control and survival who received RT within 60 days of surgery or later.

**Dunst J et al**
Improved local control in CESS 86 over CESS 81 timing of RT was brought forward from the 18th week to the 10th week

Dunst J, Results of CESS 81 and CESS 86. Cancer 1991;67:2818–2825
DOES PORT ACTUALLY BENEFIT PATIENTS WITH POOR RESPONSE TO CHEMOTHERAPY?

The EICESS 92 – first cooperative group include poor histologic response (<90% necrosis) as an indication for PORT even with clear surgical margins.

Reduction in local failures (5% vs. 12%) in the poor responders if they received PORT

Schuck A: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. IJROBP 2003;55:168–177.
<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross or microscopic positive margins</td>
</tr>
<tr>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 6–8 weeks of surgery (though there is no evidence to suggest that a further delay leads to inferior outcomes)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 Gy to the pre-chemotherapy volume</td>
</tr>
<tr>
<td>10.8 Gy boost to areas of gross tumor residual</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard daily fractionation of 1.8 Gy per fraction</td>
</tr>
<tr>
<td>Hyperfractionated RT (with equivalent total dose) may be used to reduce long term side effects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target volume</th>
</tr>
</thead>
<tbody>
<tr>
<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>Boost phase (10.8 Gy): post-operative gross residual disease with 1.5–2 cm margins</td>
</tr>
</tbody>
</table>
MANAGEMENT OF PULMONARY METASTASES

• Whole Lung Irradiation
  – Biologic effect observed in randomized trials following 1500-1800 rads in non-metastatic patients in IESS-1
    • 5 yr. RFS
      – VACA 60%>
      – VAC + Pulm XRT 44%
      – VAC 24%
      (Nesbit 1990)
  – Dose response effect reported between 12-21Gy (Dunst, 1993) using historical, non-randomized analyses

  – Retrospective Analysis of CESS 81, CESS 86, CESS 92 (Paulssen, JCO 1998)
    • Improved survival in patients with metastatic disease who receive whole lung irradiation
    • Independent prognostic factor in Cox analysis but not logistic regression analysis
  – Long term morbidity not well defined
  – Standard treatment arm on current EuroEwing’s Trial for patients with pulmonary metastases
WHOLE LUNG RT (LUNG BATH) FOR LUNG METS

- Analysis EI-CESS 92 trial

- Lung Mets (5 year EFS):
  - WLI EFS 47%
  - Without WLI 24%
RADIATION PLANNING OF CRITICAL IMPORTANCE IN THE TREATMENT OF EWING’S SARCOMA (CESS-81)

Sauer et al., Radiotherapy and oncology, 1987

S Laskar ICRO July 2015
SECOND MALIGNANCIES AFTER RADIOTHERAPY

P=0.002

Adapted from Kuttesch, JCO, 1997
PNET LEFT FEMUR
RT PORTAL MARKED ON PATIENT

RT SIMULATION FILM

RT DOSE: 45-55Gy

S Laskar ICRO July 2015
NORMAL TISSUE SPARING USING ADVANCED TECHNIQUES
RT DOSE ESCALATION USING ADVANCED TECHNIQUES

S Laskar ICRO July 2015
SUMMARY & CONCLUSIONS

- Ewing's sarcoma is best managed with multimodality approach comprising multiagent chemotherapy & local therapy (Surgery/ Radiotherapy).

- Organ & function preserving surgery remains the standard local therapy wherever feasible with negative surgical margins.

- Radiation therapy forms an important component of therapy for achieving optimal local control.

- Definitive radiation therapy in patients with surgically inoperable disease can result in good local controls with the use of optimal dose & technique.

- Adverse effects of radiation can be reduced significantly using modern radiotherapy techniques like 3D-CRT, IMRT, & Proton beam therapy.