Radiotherapy Considerations in Extremity Sarcoma

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Role of RT in STS

- Local tumour eradication while allowing successful limb preservation leading to good functional outcome with minimum toxicity
- How?
  - Reducing the risk of local recurrence by “extending” the surgical margin
- Expect 90% local control in conjunction with conservative surgery
Evidence for RT

• Overall survival not compromised by WLE + RT vs. amputation
  
  *Rosenberg et al Ann Surg, 1982*

• Local control better with WLE + BRT vs WLE for high grade tumours
  
  *Pisters et al JCO, 1996*

• Local control better with WLE + EBRT vs. WLE regardless of grade
  
  *Yang et al JCO, 1998*
Brachytherapy requires:

- Pre-procedure planning and coordination
- Experience in performing these procedures
- Multidisciplinary collaboration between radiation and surgical oncologists together with medical imaging

Orientation and geometry of brachytherapy catheters influenced by the surgical incision and reconstruction
BRT results

Cohort of extremity STS
202 pts
Adjuvant BRT

146 pts
Lower extremity

56 pts
Upper extremity

TABLE 3. Local control

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>5-y LC (%)</th>
<th>P value</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>60</td>
<td>86</td>
<td>.3</td>
<td>76–96</td>
</tr>
<tr>
<td>&gt;50</td>
<td>142</td>
<td>83</td>
<td></td>
<td>76–90</td>
</tr>
<tr>
<td>Depth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>27</td>
<td>88</td>
<td>.5</td>
<td>77–99</td>
</tr>
<tr>
<td>Deep</td>
<td>175</td>
<td>83</td>
<td></td>
<td>77–89</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Upper extremity</td>
<td>56</td>
<td>66</td>
<td>&lt;.001</td>
<td>52–80</td>
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<tr>
<td>Lower extremity</td>
<td>146</td>
<td>91</td>
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<td>86–96</td>
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<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Central</td>
<td>25</td>
<td>57</td>
<td>&lt;.001</td>
<td>38–78</td>
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<tr>
<td>Noncentral</td>
<td>177</td>
<td>88</td>
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<td>82–94</td>
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<td>Margin</td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>165</td>
<td>86</td>
<td>.04</td>
<td>81–83</td>
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<tr>
<td>Positive</td>
<td>37</td>
<td>74</td>
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<td>58–90</td>
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LC, local control; CI, confidence interval.

Fig. 5. Actuarial complications for primary high-grade sarcoma treated with brachytherapy. *Only patients who did not have nerve resection were included.
EBRT Timing

Treatment Sequencing Trade-Off Issues

Preop RT
- Lower dose (50 Gy)
- Smaller field size
- Reduced fibrosis
- Reduced edema
- Increased wound complications (35%)

Postop RT
- Higher dose (60-66 Gy)
- Larger field size
- Increased fibrosis
- Increased edema
- Wound complication risk as high as 17%

Pisters, O’Sullivan and Maki et al JCO, 2007
NCIC ‘SR2’

*O’Sullivan et al Lancet, 2002*

**EXTREMITY STS**

180 Pts*

WLE

Postop RT

92 Pts

66 Gy

Preop RT

88 Pts

50 Gy

*Designed to compare toxicity
Volume 5cm/2cm longitudinal/radial margin to 50 Gy then 2cm margin to 66 Gy

Acute wound healing complications
17% (postop) vs. 35% (preop),
p=0.01 (seen more in lower extremity)

O’Sullivan et al ASCO, 2004
**Toxicity**

- Disadvantage to pre-op RT in early stages (6 weeks) of recovery following limb preservation.
- With time (1 year) scores are similar for both treatment groups:
  - TESS (physical disability),
  - MSTS (clinical measures)  
  
  Davis et al JCO, 2002
- SF-36 bodily pain

### 2-year Late Complications (>= grade 2)

<table>
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<tr>
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<th>Pre-op RT</th>
<th>Post-op RT</th>
<th>p</th>
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<tr>
<td>Fibrosis</td>
<td>31.5%</td>
<td>48.2%</td>
<td>0.07</td>
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<tr>
<td>Stiffness</td>
<td>17.8%</td>
<td>23.2%</td>
<td>0.51</td>
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<tr>
<td>Edema</td>
<td>15.1%</td>
<td>23.2%</td>
<td>0.26</td>
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Davis et al Radiother Oncol, 2005

O’Sullivan et al ASCO, 2004

Correlates with increasing field size and dose
Fractures following radiotherapy and limb-salvage surgery for lower extremity soft-tissue sarcomas

A comparison of high-dose and low-dose radiotherapy

<table>
<thead>
<tr>
<th>Fracture rates:</th>
<th>Crude rates</th>
<th>5-yr frequency</th>
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<tbody>
<tr>
<td>Overall</td>
<td>6.3 %</td>
<td>4 %</td>
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<tr>
<td>High-dose (60-66 Gy)</td>
<td>10 %</td>
<td>7 %</td>
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<tr>
<td>Low-dose (50 Gy, mostly pre-op)</td>
<td>2 %</td>
<td>0.6 %</td>
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</table>

Females (6% vs. 2%, p = 0.02); > 55 yr (7% vs. 1%, p = 0.004)

Age, gender, and RT independent factors

Median fracture time: 44 months (range 12-153)

Holt et al. JBJS 2005
“Randomised trial of Volume of post-operative Radiotherapy given to adult patients with Extremity soft tissue sarcoma”

NCRI UK

Post-op (64-66 Gy)

End-points: Local control and function (TESS)

Sx

2 cm longitudinal margin

5 cm longitudinal margin
Fig. 2. Dose-volume histogram displaying dose to flaps (green lines) and clinical target volume (purple lines) for original (dashed line), conformal (thin solid line), and intensity-modulated radiotherapy (IMRT) (thick solid lines) plans for Patient 8. Roughly 22% of flaps received ≥40 Gy for this IMRT plan compared with almost 50% in original and conformal plans.

Fig. 3. Dose-volume histogram displaying dose to bone (brown lines) and clinical target volume (purple lines) for original (dashed line), conformal (thin solid line), and intensity-modulated radiotherapy (IMRT) (thick solid lines) plans for Patient 8. Almost 30% of bone received ≥40 Gy in original and conformal plans compared with 12% in IMRT plan.
Modern Imaging and RT Opportunities

**IMRT**
- Smaller PTVs
- Bone + skin flap avoidance
- Steep dose gradients

**Pre-op IMRT**

**Post-op IMRT**

**Older patient**

**Avoid wound problems**

**Phase 1**

**Phase 2**

**Post-op IMRT (bone avoidance)**

*Courtesy O’Sullivan/Ferguson*
Ongoing trial: “Flap-sparing” IMRT

• Phase II preop IMRT study commenced July 2005 at PMH
• Primary endpoint: Acute wound healing complications (reduce to the base line level of the NCIC SR2)
• 59 patients planned
Multidisciplinary treatment decision for pre-op RT

Positioning
Immobilization
Documentation

Contouring
Beam placement
Plan review

CT Simulation

Generation of IMRT Distribution

Treatment unit Preparation

Treatment delivery with daily image guidance

Integrate RT target back to the surgical approach
Considerations

- Anatomically diverse presentations
- Tumour size
- Volume changes during treatment course
- Position of unaffected limb
- Shifts from stable setup point to planned isocentre

Critical structures:
- Bone
- Subcutaneous tissues

Target structures:
- GTV, CTV, PTV
- Contaminated Biopsy

Deviation in setup:
- Geographic miss
- Critical structures enter high dose region
3D image guidance for RT

• Verify the isocentre position
• Identify changes in limb position
• Soft tissue delineation
• Daily assessment of volume changes
Conclusion

- Radiotherapy in extremity STS requires multidisciplinary collaboration
- The goal of functional limb preservation with local control and minimal toxicity is achievable
- “Advanced” RT is enhanced by modern imaging both for treatment planning and delivery
## Acknowledgement

Princess Margaret Hospital and Mount Sinai Hospital Sarcoma Group:

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<thead>
<tr>
<th>Name</th>
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<tr>
<td>Colleen Euler</td>
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<td>Amy Parent</td>
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<td>Brian O’Sullivan</td>
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<td>Rita Kandel</td>
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<td>David Hogg</td>
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<td>Abha Gupta</td>
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Radiation Medicine Program at PMH:

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<td>Doug Moseley</td>
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<td>Mike Sharpe</td>
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<tr>
<td>Tim Craig</td>
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<td>Radiation Physics</td>
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<td>Radiation Treatment Planners and Therapists</td>
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Amputate or not

Local control

<table>
<thead>
<tr>
<th>43 pts</th>
<th>High grade STS</th>
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<tr>
<td>16 pts</td>
<td>Amputation</td>
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<tr>
<td>27 pts</td>
<td>WLE + RT</td>
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Overall survival

Rosenberg et al Ann Surg, 1982
Limb preservation with BRT

EXTERMITY/TRUNK STS
164 Pts
WLE

BRT 86 Pts
No BRT 78 Pts

Pisters et al JCO, 1996
Limb preservation with EBRT

EXTREMITY STS
91 Pts
WLE
(+ CT for high grade)

<table>
<thead>
<tr>
<th>Adjuvant RT</th>
<th>47 Pts</th>
</tr>
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<tbody>
<tr>
<td>No Adjuvant RT</td>
<td>44 Pts</td>
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Yang et al JCO, 1998