Radiotherapy for Extremity Sarcomas – New Developments

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Historical perspectives

• **Surgery** is integral to management of Extremity Soft Tissue Sarcomas (ESTS)
  – Wider the excision, lower the probability of local failure
  
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Excision</td>
<td>60-90%</td>
</tr>
<tr>
<td>Wide Excision</td>
<td>20-30%</td>
</tr>
<tr>
<td>Compartmental resection</td>
<td>10-20%</td>
</tr>
<tr>
<td>Amputation</td>
<td>0-10%</td>
</tr>
</tbody>
</table>

• Then (1970s) – 50% of ESTS patients underwent **amputation**
• Movement towards **limb preservation** through use of **reconstructive techniques** and **adjuvant RT**
• 43 patients with high grade ESTS
• 2:1 randomization between limb-sparing resection + post-operative radiotherapy (PORT) and amputation
• Results:

<table>
<thead>
<tr>
<th>Local treatment modality</th>
<th>LR (n)</th>
<th>5y DFS (%)</th>
<th>5y OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb-sparing sx + PORT (27)</td>
<td>4</td>
<td>71</td>
<td>83</td>
</tr>
<tr>
<td>Amputation (16)</td>
<td>0</td>
<td>78</td>
<td>88</td>
</tr>
</tbody>
</table>

p value 0.06 0.75 0.99

• Positive margins was the only correlate of local recurrence on multivariate analysis

Limb preservation
Amputation
Vs
Wide Excision + 60Gy

5y DFS
78% vs 71% ns

5y OS
88% vs 83% ns

5y Local Control
0/16 vs 4/27, ns.

Randomized Prospective Study of the Benefit of Adjuvant Radiation Therapy in the Treatment of Soft Tissue Sarcomas of the Extremity

- Yang et al, JCO 1998 Jan
  - 141 patients (91 high grade, 50 low grade)
  - Randomized to receive *external beam radiotherapy* (EBRT) or not
  - **High grade** received adjuvant chemotherapy
  - LF rate @ 10y
    - High grade 0% with RT, 22% without (p=0.0001)
    - Low grade also benefited (p=0.003)
  - No difference in **OS** regardless of grade

National Cancer Institute, Bethesda, MD.
Wide Excision:
NCI, Ph III. Yang. JCO 1998.

Local Control

[Graphs showing local control for high and low grade tumors with no difference in overall survival]
A Systematic Overview of Radiation Therapy Effects in Soft Tissue Sarcomas

• Strander et al, Acta Oncologica 2003
  – Systematic review of 5 RCTs, 6 prospective studies, 25 retrospective studies, 3 other articles involving 4579 patients who had RT for STS
  – Local control rate with adj RT ~ 90%
  – Conclusion: ‘Strong evidence that adjuvant radiotherapy improves the local control rate in combination with conservative surgery in the treatment of STS of extremities and trunk in patients with negative, marginal or minimal microscopic positive surgical margins.’
• Koshy et al, IJROBP May 2010
  – SEER database analysis of 6960 patients
  – OS @ 3y
    • High grade 73% w/ RT vs 63% no RT \( (p<0.001) \)
    • Low grade no significant difference
Chosing patients properly

- Factors to consider
  - Tumour grade
    - Low grade (G1)
    - Intermediate – High grade (G2-3)
  - Tumour size
    - ≤5cm (T1)
    - >5cm (T2)
  - Tumour depth
    - Superficial (a)
    - Deep (b)
  - Margins of resection
    - <1cm
    - ≥1cm
- Staging system reflects these prognostic factors
Indications

Stage I (G1)
- Surgery
- Margins
  - $\geq 1\text{cm}$ or intact fascial plane – observation*
  - $<1\text{cm}$ without intact fascial plane


$\leq 5\text{cm}$ – post-op RT

Stage II – III (G2-3)
- Surgery + RT
- Can omit RT in $\leq 5\text{cm}$, superficial lesion excised with $\geq 1\text{cm}$ margin*

<table>
<thead>
<tr>
<th>Margin</th>
<th>10y local control (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin $&lt;1\text{cm}$</td>
<td>87±6</td>
<td></td>
</tr>
<tr>
<td>Margin $\geq1\text{cm}$</td>
<td>100</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Aims of Sarcoma Treatment
- Role of RT

1. Local Control ✓
2. Survival X
3. Limb salvage ✓
4. Retaining function ✓
5. Cosmesis ✓
6. Unresectable disease ✓
7. Palliation ✓
How RT is done
Positioning
Immobilisation
Get Creative
Simulation
CT Planning

PHASE 1

PHASE 2

PHASE 3
Microscopic Extention

Radical Surgery

Adjuvant Radiation

Wide excision

Marginal excision
Target Volumes & Margins

Gross Tumour Volume (no margin)

Clinical Target Volume
Margin 5cm ↑ 2cm

Planning Target Volume
Another 0.5cm
Treatment Delivery

Daily, 5 fractions/week

**Phase I:** Wide Margins. 50Gy/25#,

**Phase II:** 2cm margins. 10Gy/5#,

**Phase III:** 1cm around margin+. 6-10 Gy
What’s new

1. Reducing Toxicity
2. Improving control
REDUCING TOXICITY

1. Preoperative RT
2. Reducing treated volume
3. IMRT/Tomo/Proton
4. Patient Selection
Timing for RT

• Traditional approach is to give RT post-operatively
  – Allows histologic examination especially of margins
  – This information directs RT dose/delivery
  – Given 4-6 weeks after surgery ideally – allow for wound healing

• Pre-operative vs post-operative RT is still debated

• Rationale of pre-op RT
  – Reduce tumour burden before resection - more conservative surgery?
  – Smaller RT fields
  – Lower RT doses
Reducing Toxicity

1. PRE-OPERATIVE RT

- Smaller volumes radiated
- Lower doses applied
- Less tissue hypoxia
- Potential downstaging

Less radiation toxicity
Preop RT:

SR-2 Trial (NCIC CTG / CSG)

- Extremity Soft tissue sarcoma (appropriate histology)
- No chemotherapy
- Any T,N0,M0
- Any grade
- Combined modality treatment needed:
  - Surgical and Radiation Oncology opinion
  - Stratification at 10 cm cut-point

Pre-op RT
- 50 Gy in 25 fractions
- Phase 2 to 66 Gy, if margins positive

Phase 1: 5 cm longitudinal
2 cm axial
Phase 2: 2 cm coverage

Post-op RT
- 50 Gy in 25 fractions
- Phase 2 to 66 Gy, all cases
Local recurrence free

>95% Control with RT

Regional / distant recurrence free

Cancer outcomes similar

Progression free survival

HR of post-op to pre-op with 95% CI Log-rank p-value
1.0 (0.7-1.6) 0.92

Disease specific survival

HR of post-op to pre-op with 95% CI Log-rank p-value
1.1 (0.7-2.0) 0.64

Cancer outcomes similar
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Preop</th>
<th>Postop</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute wound complications</td>
<td>35%</td>
<td>17%</td>
<td>.01</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>32%</td>
<td>48%</td>
<td>.07</td>
</tr>
<tr>
<td>Edema</td>
<td>15%</td>
<td>23%</td>
<td>NS</td>
</tr>
<tr>
<td>Stiffness</td>
<td>18%</td>
<td>23%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Morbidity profiles of Preop RT:

- More Acute (*recoverable*) complications
- Less Late (*permanent*) tissue effects:
Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial

- O’Sullivan et al, Lancet 2002
  - 182 ESTS patients
  - Comparing **pre-op** (50Gy in 25f) vs **post-op** (66Gy in 33f) RT
  - Primary endpoint – major **wound** complications

- **Wound complications**
  - Pre-op 35% vs Post-op 17%
  - Difference predominantly in **lower limb**

- **ASCO Update 2004**: No **difference** in local control, progression-free survival, overall survival at **MFU 6.9y**
  - Not **powered** to formally evaluate these end-points
Pre-op vs Post-op Late Morbidity

- Update in *Radiotherapy and Oncology* Apr 2005: Late complications @ 2 years

<table>
<thead>
<tr>
<th>&gt;G2</th>
<th>Post-op (%)</th>
<th>Pre-op (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>48.2</td>
<td>31.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Oedema</td>
<td>23.3</td>
<td>15.5</td>
<td>ns</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>23.2</td>
<td>17.8</td>
<td>ns</td>
</tr>
</tbody>
</table>

-Davis AM et al-

- **RT Field size** was predictive of greater rates of fibrosis and joint stiffness and marginally predictive of oedema
- Patient with significant fibrosis/oedema/joint stiffness had significantly lower **function** scores (p<0.01)
Pre-op vs Post-op - Summary

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

### Postop RT
- Higher dose (60-66Gy)
- Larger field size
- Increased fibrosis
- Increased oedema
- Wound complication risk as high as 17%
1. May require hindquarter amputation
2. May have to sacrifice the anus.
3. Sciatic Neurovascular Bundle at Risk

Offered Preop RT.
Mass showed a partial response
Underwent limb sparing surgery
Margins(-)
Reducing Toxicity

2. Reducing treatment volume?

• ‘Standard’ margin
  – 5cm prox/distal, 2cm radial

• Vortex Trial (UK, Ph III, adj RT)
  – Proximal&Distal margin: 5cm vs 2cm

• RTOG Phase II (preopRT)
  – Tumour + edema + 2cm margin
2. Reducing Volume - Vortex Trial

- Primary endpoints
  - Limb function (TESS)
  - Time to local recurrence
- TESS
  - Toronto Extremity Salvage Score
  - Patient completed measure of physical disability

### Control Arm
Conventional two-phase treatment
Total dose: 66Gy in 33#

<table>
<thead>
<tr>
<th>Weeks 1-5: 2Gy x 5 days Weekly</th>
<th>CTV(_1): 5cm margin to GTV or 1cm to the scar, whichever is longer in the cranio-caudal direction and minimum margin of 2cm axially</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6 2Gy x 5 days</td>
<td>CTV(_2): 2 cm cranio-caudal margin to GTV and minimum margin of 2cm axially</td>
</tr>
<tr>
<td>Week 7 2Gy x 3 days</td>
<td></td>
</tr>
</tbody>
</table>

### Research Arm
Single-phase treatment to CTV\(_2\) only
Total dose: 66Gy in 33#

<table>
<thead>
<tr>
<th>Weeks 1-6: 2Gy x 5 days Weekly</th>
<th>CTV(_2): 2 cm cranio-caudal margin to GTV and minimum margin of 2cm axially</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 7 2Gy x 3 days</td>
<td></td>
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</tbody>
</table>

*Randomisation
Stratified by: tumour grade, adequacy of definitive surgical clearance and centre

200 Radiotherapy planning

200
Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

- **Rationale**
  - RMH study suggested majority of recurrences in high-dose region
  - **Brachytherapy** RCT showed good control rates even though treatment volume was only 2cm beyond tumour bed
  - Pre-op vs post-op trial showed late morbidity correlated with radiotherapy field size
  - ‘Giving a high dose where you need it’

- **Recruitment** 2007 – 2013 (UK)

\[^1\] Cleator et al Sarcoma 2001
Reducing Toxicity: volume conformity

3. Intensity Modulated RT

• Multiple Beams, varying intensity

• Varying doses - boost high risk areas.

• ‘odd-shaped’ volumes, avoid critical organs
WHAT ELSE IS NEW?

- 3D-CRT
- IMRT
- IGRT
- Protons
**IMRT**

- **Spare Flap**
  - (reduce wound complications for preop RT)

- **Spare bone**
  - **Reduce fracture risk**
Intensity Modulated Radiotherapy (IMRT)

- Able to conform to the shape of intended treatment target
- Minimize dose of RT to surrounding normal structures
- Particular advantage in sparing bone which is a natural barrier to local spread

Hong et al, IJROBP 2004
Plan comparison:

<table>
<thead>
<tr>
<th></th>
<th>Conformal Plans</th>
<th>IMRT Plans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose to flap</td>
<td>40.1</td>
<td>26.7</td>
</tr>
<tr>
<td>Mean dose to bone</td>
<td>25.9</td>
<td>21.9</td>
</tr>
<tr>
<td>Mean dose to CTV</td>
<td>50.3</td>
<td>50.1</td>
</tr>
</tbody>
</table>

24 patients

(O’sullivan)
• **MSKCC retrospective** study

• 41 patients
  – 51% **positive/close** margins
  – 68% tumours >10cm
  – 83% **high grade**

• 50Gy Preop IMRT (7) or ~63Gy Postop IMRT (34)

• Complications
  – 2 (4.8%) fractures not req op
  – 32% edema (all <G3 – less than 30% discrepancy)

### Table: 5-year (%) and 95% CI

<table>
<thead>
<tr>
<th>MFU 35m</th>
<th>5-year (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC</td>
<td>94</td>
<td>86-100</td>
</tr>
<tr>
<td>DMFS</td>
<td>61</td>
<td>45-76</td>
</tr>
<tr>
<td>OS</td>
<td>64</td>
<td>45-84</td>
</tr>
</tbody>
</table>
Proton Therapy

• **Rationale**
  – 60% reduction in radiation dose to normal tissue
    • Lower dose region **proximal** to tumour
    • Uniform dose **in region** of tumour
    • Close to zero dose **beyond** tumour

• **Extensive use in skull base/spinal sarcomas**

• **Potential in ESTS**
  – Large, medial **prox** thigh tumours
    • Spare femur, hip joint, genitalia, anorectal tissues
  – **Shoulder** lesions
    • Spare lung apex, shoulder joint
Paraspinal Epithelioid Sarcoma

**IMRT**

**Protons**

Lower integral dose
Long-Term Results of a Prospective Randomized Trial of Adjuvant Brachytherapy in Soft Tissue Sarcoma

- Pisters et al, JCO 1996 Mar
  - 164 patients
  - Randomized to post-operative brachytherapy (BRT) or not
  - Freedom from local recurrence @ 5y
    - High grade 89% with BRT, 66% without (p=0.0025)
    - Low grade no impact (p=0.6)
  - No significant impact on distant metastasis or disease specific survival
Brachytherapy:
MSKCC, Ph III. Harrison. JCO 1996.

42-46Gy LDR, from 6\(^{th}\) POD. (Benefit for High Grade only).
Local Control Comparison of Adjuvant Brachytherapy to Intensity-Modulated Radiotherapy in Primary High-Grade Sarcoma of the Extremity

Kaled M. Alektiar, MD; Murray F. Brennan, MD; and Samuel Singer, MD

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>BRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size &gt;10cm</td>
<td>48</td>
<td>30</td>
<td>.005</td>
</tr>
<tr>
<td>Margin +/-close</td>
<td>49</td>
<td>20</td>
<td>.006</td>
</tr>
<tr>
<td>Periosteal/bone resection</td>
<td>30</td>
<td>13</td>
<td>.02</td>
</tr>
<tr>
<td>Nerve resection</td>
<td>54</td>
<td>14</td>
<td>.002</td>
</tr>
<tr>
<td>5y LC</td>
<td>92</td>
<td>81</td>
<td>.04</td>
</tr>
</tbody>
</table>

‘On multi-variate analysis, IMRT was the only predictor of improved local control’

BRACHYTHERAPY
- Why brachytherapy

Advantage
- high doses to tumour bed
- Low overall dose to normal tissues

Role
• As main RT
• As boost in combination with EBRT
• Re-treatment, after previous EBRT
Interstitial Brachytherapy
Reducing Toxicity

4. Patient Selection

Can we avoid RT?

Series:
Rydholm JCO 1991. LRR 7%
Baldini JCO 1999. LRR 10%
Alektiar JCO 2002. LRR 20% (no RT), 16% (with RT)

Randomised:
NCI JCO 1998. LRR 28% (no RT), 2% (with RT)
Indications for Adjuvant RT

1. All High Grade STS.

2. Low-Int Grade STS with close or positive margins.

3. Tumour recurrence
SUMMARY:
Where we are

• Excellent local control (80-90%) with wide excision and adjuvant RT
• Most High grade STS should receive adjuvant RT
• Low Grade lesions with close/positive margins, or where local recurrence is morbid.
• Preoperative RT should be considered:
  – Reducing late toxicity
  – For downstaging (near critical structures)
  – Cancer outcome preserved
Summary – ESTS + RT

• Radiotherapy reduces local recurrence rates after limb sparing surgery, with good functional result
  – High grade – 10%
  – Low grade – 0-10%
• No RCT evidence that it improves overall survival
• Optimal radiotherapy volume is still under investigation
• Pre-operative radiotherapy may afford better functional sequelae without compromising local control
• Advances in RT (IMRT, IGRT, protons) can potentially reduce morbidity while maintaining local control rates
Thank You.
Appendix

• Pre-op RT
  – Single Phase Treatment to 50Gy

• Post-op RT
  – 2 phases
    • Wide ‘elective’ phase to 50Gy
      – Scar and drain exit included
    • Narrower ‘boost’ phase to 10Gy, or 16Gy in the case of microscopic positive margins
Pre-op RT – Single phase

Pre-op tumour
Peritumoral edema

0.7-1cm
1.5cm
4cm
FEMUR
Post-op RT – Elective phase

Scar
Pre-op tumour
Surgical bed

0.7-1cm

1.5cm

FEMUR

4cm
Post-op RT – Boost phase

Scar
Pre-op tumour
Surgical bed

0.7-1cm
1.5cm
2cm
FEMUR