Organ sparing Brachytherapy in soft tissue sarcomas -- Evidence & Planning

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FRCR (Clinical Oncology),
Clinical Fellow, Extracranial SBRT, Ottawa, Canada
- Varied locations
- Distinct HP types

<table>
<thead>
<tr>
<th>T Primary tumor</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 5 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Superficial tumor</td>
</tr>
<tr>
<td>T1b</td>
<td>Deep tumor</td>
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<tr>
<td>T2</td>
<td>Tumor greater than 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T2a</td>
<td>Superficial tumor</td>
</tr>
<tr>
<td>T2b</td>
<td>Deep tumor</td>
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<table>
<thead>
<tr>
<th>N Regional lymph nodes</th>
<th>Description</th>
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<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
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<tr>
<td>NO</td>
<td>No regional lymph nodes metastases</td>
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<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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<table>
<thead>
<tr>
<th>M Distant metastasis</th>
<th>Description</th>
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<tbody>
<tr>
<td>MO</td>
<td>No distant metastasis</td>
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<tr>
<td>MI</td>
<td>Distant metastasis</td>
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<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>G1, GX</td>
<td>T1a-1b</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>G1, GX</td>
<td>T2a-2b</td>
</tr>
<tr>
<td>II</td>
<td>A</td>
<td>G2, G3</td>
<td>T1a-1b</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>G2</td>
<td>T2a-2b</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>G3</td>
<td>T2a-2b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any G</td>
<td>Any T</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>Any G</td>
<td>Any T</td>
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</table>
Surgery - primary definitive treatment

LRR - 5-20%

LRR - 30-60%
The Treatment of Soft-tissue Sarcomas of the Extremities

Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjuvant Chemotherapy

STEVEN A. ROSENBERG, M.D., Ph.D.,* JOEL TEPPER, M.D.,† ELI GLATSTEIN, M.D.,† JOSE COSTA, M.D.,‡ ALAN BAKER, M.D., MURRAY BRENNAN, M.D.,* ERNEST V. DEMOSS, M.D.,* CLAUDIA SEIPP, R.N.,* WILLIAM F. SINDELAR, M.D., Ph.D.,* PAUL SUGARBAKER, M.D.,* ROBERT WESLEY, Ph.D.§

Between May 1975 and April 1981, 43 adult patients with high-grade soft tissue sarcomas of the extremities were prospectively randomized to receive either amputation at or above the joint proximal to the tumor, including all involved muscle groups, or to receive a limb-sparing resection plus adjuvant radiation therapy. The limb-sparing resection group received wide local excision followed by 5000 rads to the entire anatomic area at risk for local spread and 6000 to 7000 rads to the tumor bed.

From the National Cancer Institute, Bethesda, Maryland

SOFT-TISSUE SARCOMAS are malignant tumors that arise in the extraskeletal connective tissues of the body. Though a large number of different pathologic

-Equivalent Disease specific survival
Barring T1A, low grade, negative margins (>1cm),

All require radiation therapy

EBRT  Brachy
Brachytherapy

**Advantages**

- As applicators in tumour bed - high dose to target and rapid dose fall off - reduced dose to normal tissues
- This could translate to lower risk of lymphedema/subcut fibrosis/ bone fracture
- Short duration of treatment
- Early treatment in post op period has shown to improve LC (avoiding tumour repopulation, efficacy in less hypovascular/ fibrosed tumour)

**Disadvantages**

- Limited as compared to EBRT in its volume coverage
- Depends on skill of the radiation oncologist
Evidence
- Local control was significantly better with BT in high grade tumours
- No difference in local control of low grade tumours
- No difference in Distant metastases free period
- No difference in disease specific period
- Retrospective
- Most common were spindle cell sarcomas f/b liposarcomas

- For brachytherapy alone- Local control was 75%, improved to 82% after salvage (med f/u -30 mos)
- For brachytherapy+EBRT, LC was 71% which after including salvaged patients- rose to 86%.

- Treatment related complications <1%
Perioperative Interstitial Brachytherapy for Soft Tissue Sarcomas: Prognostic Factors and Long-Term Results of 155 Patients

Siddhartha Laskar, MD, Gaurav Bahl, MD, Ajay Puri, MS, Manish G. Agarwal, MS, MaryAnn Muckaden, MD, Nikhilesh Patil, MD, Nirmala Jambhekar, MD, Sudeep Gupta, DM, Deepak D. Deshpande, PhD, Shyam K. Shrivastava, MD, and Ketayun A. Dinshaw, FRCR

155 adults with STS treated with Sx, BT with/without EBRT

Cumulative Radiotherapy dose > 60Gy had a significant positive impact on

- Local Control
- Disease Free Survival
- Overall Survival
Indications for Brachytherapy as monotherapy

- Medium sized tumours (<10cms)
- High grade
- Negative surgical margins
- Preferable primary lesion

- Re-irradiation
- Paediatric STS
Brachytherapy + EBRT

EBRT will add to benefit along with Brachytherapy in:

• BT cannot adequately cover
  - unfavourable geometry/ OAR restriction
  - skin ulcer

• High risk of recurrences
  - >10cms
  - positive margins
  - recurrent disease
  - deep location
HDR brachytherapy alone in post-op soft tissue sarcomas with close or positive margins. Jun Itami et al, (Japan) Brachytherapy, 2009

The local recurrence free survival was 43.8% if the patient had positive margin or a recurrent lesion vs 93.3% if it was a primary lesion with adequate margin.

In Group 1 lesions, addition of a wide field EBRT seems to be necessary to improve the local control rate.

Also, evidence for EBRT boost in positive margins by Alekhteyar et al IJROBP 1996
<table>
<thead>
<tr>
<th>Author (year) [reference number]</th>
<th>Institute</th>
<th>Inclusion criteria (n)</th>
<th>EBRT dose (Gy) Median (range)</th>
<th>BT dose (Gy) Median (range)</th>
<th>Local control (%)</th>
<th>Survival</th>
<th>Complication rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiu et al. (1991) [7],</td>
<td>Memorial Sloan-Kettering Cancer Centre, USA</td>
<td>Locally advanced/candidate for amputation (33)</td>
<td>–</td>
<td>LDR 44 (25-54)</td>
<td>At 3 yr, 88%</td>
<td>–</td>
<td>39% (overall)</td>
</tr>
<tr>
<td>Harrison et al. (1993) [8],</td>
<td>Memorial Sloan-Kettering Cancer Centre, USA</td>
<td>After gross tumor resection BT (intra-operative insertion) vs. no BT, randomized control trial (166)</td>
<td>–</td>
<td>LDR 42-45</td>
<td>At 5 yrs, 82% vs. 67%</td>
<td>5 yr DFS 81% vs. 80% (NS)</td>
<td>14% vs. 10% (NS) (wound complication)</td>
</tr>
<tr>
<td>Chaudhary et al. (1998) [9],</td>
<td>Tata Memorial Hospital, India</td>
<td>Non-metastatic STS in adults (177)</td>
<td>45 (12-70)</td>
<td>HDR alone 30 (29-50)</td>
<td>At 30 months, 70%, After salvage, 86%</td>
<td>–</td>
<td>&lt; 1%</td>
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<tr>
<td>Rosenblatt et al. (2003) [10],</td>
<td>Haifa, Israel</td>
<td>Non-metastatic STS (32)</td>
<td>39.2 (16.2-45)</td>
<td>LDR 33 (18-49), HDR 16</td>
<td>At 3 yrs, 87.5%</td>
<td>At 5 yrs DFS 56%, OS 70%</td>
<td>Wound complication 16%, Late local toxicities 19%</td>
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<tr>
<td>Laskar et al. (2007) [11],</td>
<td>Tata Memorial Hospital, India</td>
<td>Non-metastatic STS, children, (median age 13 yrs) (50)</td>
<td>45 (30.6-45)</td>
<td>HDR alone 36 (30-40) EBRT + HDR BT 21 (15-36)</td>
<td>At 51 months, 82%</td>
<td>At 51 months, DFS 68%, OS 71%</td>
<td>Wound complication 4%, Late toxicities 20%</td>
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<tr>
<td>Laskar et al. (2014) [12],</td>
<td>Tata Memorial Hospital, India</td>
<td>Non-metastatic STS, children, (Median age 15 yrs) (76)</td>
<td>–</td>
<td>–</td>
<td>At 70 months, 85%</td>
<td>At 70 months, DFS 74%, OS 77%</td>
<td>Wound complication 8%, Late local toxicities 31%</td>
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<tr>
<td>Cortesy et al. (2017) [13],</td>
<td>Italy</td>
<td>Primary or recurrent STS (107)</td>
<td>46 (mean)</td>
<td>LDR and PDR 20 (mean?)</td>
<td>At 5 yrs, 80.5%</td>
<td>At 5 yrs, DFS 58.6%, OS 87.4%</td>
<td>–</td>
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<tr>
<td>Current study</td>
<td>Primary STS (27)</td>
<td>50 (30-50)</td>
<td>HDR alone 60.7 (33.4-67.4) EBRT + HDR BT 66.6 (42-78)</td>
<td>At 5 yrs, 85.7%</td>
<td>DFS 39.7 ± 3.9 months OS 42.4 ± 3.4 months</td>
<td>≥ grade 2 skin toxicity in 14.8% patients</td>
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<tr>
<td>Specific situation</td>
<td>Preferred treatment</td>
<td>Treatment considerations</td>
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<td>Extremity/trunk</td>
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<tr>
<td>Low grade: Superficial, &lt;5 cm, and wide margin (≥1 cm)</td>
<td>Surgery alone</td>
<td>Limb-sparing surgery</td>
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<td>High grade: &lt;10 cm and negative margin</td>
<td>BT alone</td>
<td>30–50 Gy</td>
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<tr>
<td>Low grade: deep, &gt;5 cm, or negative margins (&lt;1 cm)</td>
<td>BT + EBRT</td>
<td>BT + EBRT &gt;60 Gy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High grade: &gt;10 cm, negative margin</td>
<td>BT + EBRT</td>
<td>BT + EBRT ≥65 Gy</td>
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<tr>
<td>All grades: close/positive margin</td>
<td>BT + EBRT</td>
<td>BT + EBRT ≥65 Gy</td>
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<tr>
<td>Recurrent (not previously radiated)</td>
<td>BT + EBRT</td>
<td>BT + EBRT ≥65 Gy</td>
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<tr>
<td>Re-irradiation</td>
<td>BT alone</td>
<td>30–50 Gy</td>
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ABS, Naghavi et al, Brachytherapy, 2017
When not to do Brachytherapy?

• Location very close to skin/ skin compromised
• Bone (periosteum removed) and exposed
• Irregular tumour bed with doubtful catheter stability/ possibility of kink
• Acral and phalangeal sites
Procedure and Planning
Pre-procedure work-up

**General pat. assessment** - tolerance of treatment (PS, comorbidities, prev RT)
- Limb function
- Risk of wound complications (DM, baseline edema)

**Evaluation of primary**
- Imaging - disease extent, resectability, relation to bone/neurovascular bundle
  - Commonly MRI.

**Biopsy** - carefully planned, by same surgeon

**Nodal evaluation** - in
- S-ynovial sarcoma
- C-lear cell sarcoma
- A-ngiosarcoma
- R-habdomyosarcoma
- E-pitheloid sarcoma

**Evaluation for Distant metastases** -
- Chest CT for all.
- Histopathology based abdominopelvic/CNS imaging
Most commonly, catheters inserted intra-operatively during surgical resection

Surgeon places clips to demarcate tumour bed and any areas at high risk or to demarcate critical structure, eg. - NVB
Hollow flexible plastic catheters are placed with the aid of steel needles over the tumour bed.

- Can be along or perpendicular to incision line.
- Parallel placement

- 1-1.5cms separation

- Avoid penetrating blood vessels

- Pass through the tumour bed (Sutures to stabilize catheters to tumour bed)
Avoid direct contact to bones and nerves

May consider muscle/gelfoam/bone wax (maintaining 0.5cms distance)— Mison Chun et al, JJCO 2001

Commonly, single plane is sufficient
• Entry and exit points of the catheters should be kept 2 cm away from incision line.

• Buttons/balls to be placed in both ends of the catheters.

• Adequate gap of 5 mm between end buttons and skin to encompass post-operative tissue edema.
After a gap of 4-6 days,

Planning CT scan is done – 2.5 - 3 mm thickness
Adjust position accordingly that applicator
digitization is not difficult.

Measurement and cutting of applicators to remove
the dummy, numbering. Followed by digitization
BT- CTV consists of the surgical bed with a margin,
- ≥ 2 cm craniocaudally
- 1-2 cm laterally
- scar and drain sites not included
- Clips defining tumour bed help

No PTV expansion in BT

Contour appropriate OARs (bone, skin, NVB, where applicable)
EBRT delineation will be more generous with greater longitudinal margin, including scar and drain sites.

Longitudinal margin to tumour bed while placing applicators in BT can be accordingly modified.
### Dose and Boost Recommendations

- **Dose**: 3-4 Gy/fractions
- **Boost**: 6 fractions, Brachy alone- 10-12 fractions

Recommendations: 36 Gy/10 Fr definitive and 18-21 Gy/6-7 fr as boost

<table>
<thead>
<tr>
<th>BT type</th>
<th>Modality</th>
<th>EBRT (Gy)</th>
<th>BT (Gy)</th>
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<tr>
<td>LDR/PDR</td>
<td>BT</td>
<td>45-50</td>
<td>45-50</td>
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<tr>
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<td>BT + EBRT</td>
<td>45-50</td>
<td>15-25</td>
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<tr>
<td>HDR</td>
<td>BT</td>
<td>30-50</td>
<td>30-50</td>
</tr>
<tr>
<td></td>
<td>BT + EBRT</td>
<td>45-50</td>
<td>12-20</td>
</tr>
<tr>
<td>IORT</td>
<td>IORT + EBRT</td>
<td>45-50</td>
<td>10-20</td>
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</table>
DHI = \[ \frac{V_{100} - V_{150}}{V_{100}} \]; 0.8 means 80% of volume receiving 100-150% of the prescribed dose and <20% of the volume receiving >150%
Alternately, visualizing isodoses of 150% and 200% for overlap
OAR should receive < 100% of prescription dose, unless required i/v/o tumor involvement.

To minimize skin toxicity,

- the dose to the skin should be less than \( \frac{2}{3} \)rd the prescribed dose
- Source loading should be \( \geq 0.5 \) cm from skin
Dwell >5 mm from surface

Avoid overlap of 200% isodose line

Skin ≤ 2/3 dose
Site care

• Avoid major movements to prevent kinks

• Do not wet

• Antiseptic ointment

• Removal procedure
Side effects

Acute

Wound related complications- dehiscence/ gaping/edema (Skin- tautness during procedure and wound closure)

Wound complications can be reduced by treating 5 days post surgery and catheter insertion

Local pain and erythema at site for few days, generally self-resolving

Alektiar et al, IJROBP 2000
Chronic

- Hypo pigmentation
- Telangiectasia
- Skin atrophy
- Subcutaneous fibrosis
- Stiffness at site, joint stiffness
- Neuropathy (cumulative LDR dose >90Gy; gel foam)*
- Bone fracture (<5% risk, related to periostoeal stripping)

*Zelefsky et al IJROBP 1990
Complications depend on-----

- Total treatment dose
- BT dose, BT dose per fraction
- No of catheters, Tumour volume-150
- Addition of EBRT (fibrosis, chronic edema, joint)
  Emory et al 2012; Laskar et al 2007
- Lower limb as compared to upper limb
- Joint proximity
- Acral/distal lesions
- Reirradiation
THANK YOU

ROMANS 1:8
Acknowledgements

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