Sarcoma: Benefit From Brachytherapy in Curative Intention

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Disclosure

Antonio Cássio Assis Pellizzon, MD, PhD, MSc, does not have any financial relationships or products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

Learning Objectives

• This session will discuss:
  - Tumor staging
  - Surgery indication
  - Brachytherapy techniques
  - Results
  - Complications of treatments
Incidence

- Rare: for 2013 –
  - 11,400 diagnoses of STS
  - 3,000 bone sarcomas

- Deaths
  - 4,400 (STS) and 1,440 (bone) expected

- Mesodermal origin

Overview

- A variety of radiotherapeutic approaches have been used in the local management of STS
- Randomized trials comparing brachytherapy (BT) and external beam radiation therapy (EBRT) in STS have not been published
Etiology

- Previous Radiation (increased)
  - Grade of tumors
  - Risk for metastasis
- Chemical exposure
  - Thorotrast, vinyl chloride, arsenic for hepatic angiosarcoma
- Genetic syndromes
  - Neurofibromatosis – nerve sheath tumors
  - Familial gastrointestinal stromal tumor syndrome – KIT mutation
  - Skin hyperpigmentation, urticaria, cutaneous mast cell dx

Location and Type

Perez and Brady’s Principles and Practice of Radiation Oncology, 6th Ed
Classification

• Bone
• Soft tissue
  – Visceral – gastrointestinal, genitourinary, and gynecologic organs
  – Nonvisceral – soft tissues (muscle, tendon, adipose, pleura, and connective tissue)

Staging

• Does not take into account extremity vs. visceral
  ➔ Predicts survival and risk of metastasis, but not local recurrence

• AJCC/UICC Staging System for STS
  • T1: <5 cm
    – T1a: Superficial to muscular fascia
    – T1b: Deep to muscular fascia
  • T2: >5 cm
    – T2a: Superficial to muscular fascia
    – T2b: Deep to muscular fascia

N0 X N1: Regional nodal involvement
Grading
  G1: Well-differentiated
  G2: Moderately differentiated
  G3: Poorly differentiated
  G4: Undifferentiated

Staging

<table>
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<th>G</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tr>
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</table>


Relative Risk for Local Recurrence

- High-grade - 4.3
- Deep location - 2.5
- Local recurrence at presentation - 2.0
- Size 5.0–10.0 cm - 1.9
- Microscopically positive margin - 1.8
- Age >50 years - 1.6
- Size >10.0 cm - 1.5

Surgery – Gold Standard

- Limb-sparing vs. amputation → No survival difference
- Limb sparing + radiation

- Amputation may still be indicated for:
  - Neurovascular involvement
  - Bone involvement
  - Function non-preservation

Resection

- Arbitrary margin – >2 cm
  - Presence of positive margins → increases local recurrence by 10%–15%
- No need for lymph node dissection
  - Only 2%–3% of nodal metastasis
Adjuvant Treatment Indications

- Will depend on
  - Anatomical location
  - Surgical indication
  - Stage
  - Resectability
  - Margins

Treatment Options – Stages IA, IB, IIA

- Surgical excision — treatment of choice
  - Margins >2 cm in all directions
- Low metastatic potential
  - RxT or CHT is usually not given as adjuvant

Treatment Options – Stages IA, IB, IIA

**Margins**

> 2 cm → may not require radiation (low grade)

1-2 cm – as above (?)

<1 cm → Re-resection or adjuvant EBRT and/or BT(?) recommended to prevent LR associated with improved 5-y DFS

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**Stages IIIB, IIC, III**

- Pre-operative or post-operative RT
  - In some instances neoadjuvant CHT + RT

- Pre-op – downsize → limb-sparing resections

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Treatment Recommendations for High-Grade STS and all Stages II-III

→ High risk of recurrence
→ Potential metastases

• Resectable disease
  – Surgery followed by RT with or without adjuvant CHT
  – Surgery alone
  – Preoperative RT with or without CHT

• Unresectable disease
  – Preoperative or definitive RT with or without CHT with doxorubicin-based regimens

Pre-op or Post-op Radiation?

• Pre-op → increased wound complications (debatable)
  – 35% vs. 17%
  – Risk confined to lower extremity
• Pre-op → may be better for
  – Upper extremity and H&N
  – Equal wound complication risk
  – Benefit of lower RT doses to more vital tissues

Pre-operative RT

Benefits
- Large retroperitoneal or inguinal tumors may become resectable
- A smaller treatment field is needed
- Potentially less tumor seeding may occur during resection

Negative aspects $\rightarrow$ increased wound-healing complications

Margins close $-$ (<1 cm) or positive, consider boost with
- BT
- IORT
- EBRT

Pre-Op vs. Post-Op RT

- Retrospective study
- 517 cases (246 post-op vs 271 pre-op RT)
- No difference in 5- and 10-year survival rates (81% and 78%, respectively)
- 10-year incidence of complications for post-operative RT (9% vs 5%; $P = 0.03$)
Timing for RXT

- >60–120 days: worse survival
- Retrospective analysis
  - 102 patients
- Short delay (<4 months) vs long delay
  - 5-year – LC favored short delay
  - 88% vs 62% ($P = 0.048$)


Brachytherapy

- Potential radiobiological advantages of brachytherapy include
  - Reductions in normal tissue doses decreasing
    - Probability of growth deformity
    - Dose of EBRT required
    - Rate of 2nd tumor formation
Techniques

• HDR - Interstitial
• Afterloading catheters
  – Inserted in the tumor bed

  • One or two plans
  • 1.0-1.5 cm distant
  • Preferably transverse to the muscle
  • Catheters can be sutured to maintain equidistance between each other
Literature Review

**Radiation Oncology**

Research

*High-dose-rate brachytherapy for soft tissue sarcoma in children: a single institution experience*

Gustavo A Viani*1, Paulo E Novaes1, Alexandre A Jacinto1, Celia B Antonelli2, Antonio Cassio A Pellizzon1, Elisa Y Saito1 and João V Salvajoli1

18 pediatric patients
Male – 5  x  Female – 13

Viani et al.

<table>
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<tr>
<th>Patient/Stage</th>
<th>Diagnosis</th>
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<th>Implant size</th>
<th>Margins</th>
<th>CHT</th>
<th>Group</th>
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*Intergroup Rhabdomyosarcoma Study (IRS) staging used for both rhabdomyosarcomas and alveolar soft part sarcomas. ASPS= soft tissue sarcomas alveolar, RMSE= Rhabdomyosarcoma embryonal.

Viani et al.

<table>
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<tr>
<th>Local control (%)</th>
<th>Distant failure (%)</th>
<th>Overall survival (%)</th>
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<td>Overall</td>
<td>94.5 (37/18)</td>
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<td>Margins</td>
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<td>100 (11/1)</td>
<td>85.7 (6/7)</td>
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<td>(1/1)</td>
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<td>92.8 (3/14)</td>
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<td>(6/7)</td>
<td>(4/3)</td>
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<td>100/100</td>
<td>92.8 (3/14)</td>
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<td>(6/7)</td>
<td>(4/3)</td>
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<td></td>
<td>100/100</td>
<td>90 (1/10)</td>
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<td>(6/7)</td>
<td>25 (2/8)</td>
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<td>20 (2/10)</td>
<td>20 (2/10)</td>
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</table>

Viani et al.
HDR for STS in Children: ACCCC Experience

OS @ 5 years – 84.5%

Facts:
• No local or regional failures in the group treated with HDR alone
• Combined HDR and EBRT
  – 1 local failure (22 months)
  – 3 pulmonary metastatic disease (18, 38, and 48 months after diagnosis)

Acute Side Effects
• Skin reactions: 6 patients (33%)
• Wound dehiscence: 4 patients (22%)

Late Side Effects
• Extensive fibrosis: 3 patients (16.5%)

Acute Side Effects


HDR and Limb-Sparing Surgery for STS in Adults: ACCCC Experience

• 21 patients treated from 1993 to 1999
• EBRT:
  – Pre- or post-op 30-50 Gy
• HDR:
  – 18–36 Gy (fx) 3–6 Gy BID

Table: n, N

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<tr>
<td>arm</td>
<td>3</td>
<td>10.7</td>
</tr>
<tr>
<td>forearm</td>
<td>3</td>
<td>10.7</td>
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Results:
Actuarial @ 5 years
• LC: 85.2%
• DFS: 75%
• OS: 93.7%

Late Side Effects
• Extensive fibrosis: 1 (3.5%) (surgical correction)


Primary x Recurrent
Primary x Recurrent

- 45 patients
  - 17 primary
  - 28 recurrent
- HDR BT alone
  - 11 (mean dose 40 Gy; 30–54 Gy)
- HDR + EBRT (34 patients)
  - HDR - 34 - (mean 24 Gy; 15–30 Gy)
  - EBRT (40–50 Gy)

Petera et al

Primary x Recurrent

- LC – 100% in primary vs 64% recurrent ($P = 0.004$)
- At 5 years:
  - Overall survival: 70%
  - Local control: 74%
- Prognostic Factors
  - LC $\rightarrow$ better for extremities x trunk tumors
  - EBRT + BT better than BT alone
  - Doses >65 Gy

Petera et al
LDR x HDR


Adjuvant high-dose-rate and low-dose-rate brachytherapy with external beam radiation in soft tissue sarcoma: A comparison of outcomes

<table>
<thead>
<tr>
<th>Patient and treatment characteristics</th>
<th>LDR</th>
<th>HDR</th>
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<td>Mean age (years)</td>
<td>52</td>
<td>65</td>
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<tr>
<td>Diabetes, no. (%)</td>
<td>2 (10)</td>
<td>1 (6)</td>
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<tr>
<td>Upper extremity/lower extremity, no. (%)</td>
<td>5 (25)/14 (70)</td>
<td>8 (47)/9 (53)</td>
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<td>Stages I-II/stages III-IV, no. (%)</td>
<td>3 (15)/17 (85)</td>
<td>7 (41)/10 (60)</td>
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<tr>
<td>Grades 1-2/grade 3, no. (%)</td>
<td>7 (35)/13 (65)</td>
<td>6 (35)/11 (65)</td>
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<tr>
<td>Margin positive, no. (%)</td>
<td>3 (15)</td>
<td>2 (12)</td>
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<tr>
<td>Resection area (cm²)</td>
<td>166</td>
<td>181</td>
</tr>
<tr>
<td>Adjuvant chemotherapy, no. (%)</td>
<td>6 (30)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Known metastases, no. (%)</td>
<td>2 (10)</td>
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LDK = low-dose rate; HIK = high-dose rate.

37 patients
Pre- or post-op EBRT
+ LDR or HDR

**LDR x HDR**

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<tr>
<th>Radiation details</th>
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<td>3 (19)/14 (82)</td>
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<tr>
<td>EBTR mean (range) (cGy)</td>
<td>4005 (44-65)</td>
<td>4826 (45-50)</td>
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<tr>
<td>BT mean (range) (cGy)</td>
<td>1676 (15-20)</td>
<td>1332 (10.2-18)</td>
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<td>Total BED dose (cGy)</td>
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LDR = low-dose rate, HDR = high-dose rate; EBT = external beam radiation therapy.

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**LC @ 2 years**

- 90% LDR X 94% HDR

**Complications – Grades 2-4**

- 40% LDR vs. 18% HDR (P = NS)

**HDR group – predictive of LC**

- Dose per fraction, total BT dose, and total BED

**CONCLUSION** — HDR may have lower incidence of severe (grade ≥3) acute toxicity than LDR
### Published Data HDR

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<th>Year</th>
<th>FU mo</th>
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<td>2012</td>
<td>11</td>
<td>HDR</td>
<td>37</td>
<td>92</td>
<td>NR</td>
</tr>
<tr>
<td>San Miguel</td>
<td>2011</td>
<td>49</td>
<td>HDR + EB</td>
<td>60</td>
<td>77.4</td>
<td>28.3</td>
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</tbody>
</table>


### Nerve Tolerance to HDR in Patients With STS: A Retrospective Study

**BMC Cancer**

*Nerve tolerance to high-dose-rate brachytherapy in patients with soft tissue sarcoma: a retrospective study*

Tadahiko Kubo1, Takashi Sugita2, Shoji Shimose1, Tsushihiro Matsuo1, Ken Hiraoka1, Hiroaki Kimura3, Masahiro Kenjo4 and Mitsuo Ochi1
Nerve Tolerance to HDR in Patients With STS: A Retrospective Study

- 7 patients

- Catheters
  - Placed → tumor bed → directly upon the preserved neurovascular structures

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<table>
<thead>
<tr>
<th>No.</th>
<th>Margin</th>
<th>Planning Target Volume (cm²)</th>
<th>Brachytherapy (Gy)</th>
<th>EBRT (Gy)</th>
<th>Failure</th>
<th>Complication</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>65</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>Motor paresis</td>
<td>AWD* (77)</td>
</tr>
<tr>
<td>2</td>
<td>Negative</td>
<td>63</td>
<td>50</td>
<td>(38)</td>
<td>Local fracture</td>
<td>AWD (75)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Negative</td>
<td>52</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>AWD (82)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Negative</td>
<td>93</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>AWD (43)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Negative</td>
<td>44</td>
<td>50</td>
<td>20</td>
<td>-</td>
<td>Sensory loss</td>
<td>AWD (54)</td>
</tr>
<tr>
<td>6</td>
<td>Negative</td>
<td>40</td>
<td>50</td>
<td>-</td>
<td>Lung</td>
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<td>DOD#(72)</td>
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<td>7</td>
<td>Positive</td>
<td>134</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td></td>
<td>DOD#(13)</td>
</tr>
</tbody>
</table>

PTV= Planning target volume, EBRT= External beam radiation therapy, AWD= Alive without disease, DOD= Dead of disease, DOD#= Dead from other cause

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Nerve Tolerance to HDR in Patients With STS: A Retrospective Study

RESULTS:
• Median follow-up of 4 years
• 5-year actuarial
  – OS: 83.3%
  – DSS: 68.6%
  – LC: 83.3%
• None developed HDR-induced peripheral neuropathy


Potential Complications

• Wound complications
• Infections
• Skin reactions
• Seromas
• Catheter failures

Final Thoughts

- STS needs a relative high dose to achieve local control → BT can be one of the answers
- There is a limited number of reports on the use of PDR for STS
- There is no randomized comparison of HDR and LDR for STS
- Prospective randomized trials using HDR for STS should be encouraged