Current Management in Soft Tissue Sarcoma

Radiation Therapy for Soft Tissue Sarcoma

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30 March 2019
Scope of presentation

- Types and methods of RT delivery: WHAT
- Rationale for the use of RT: WHY
- Timing and scheduling of RT: WHEN
- RT process and techniques: HOW
- RT complication

- Extremity soft tissue sarcoma
- Retroperitoneal sarcoma

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Soft tissue sarcoma
Management by multimodality team

Case review at multi-disciplinary team
Types and methods of RT delivery
What is radiation?

- Radiation is energy that comes from a source and travels through some material or through space.
- Non-ionizing (low energy)
- Ionizing (high energy) radiation → For medical use
Radiation therapy modalities

- Teletherapy or External beam radiation therapy
  - Photon
    - eg. Co-60 machine, Linear accelerator (LINAC)
  - Particle beam
- Brachytherapy
  - eg. Ir-192 (sealed source), I-125 (unsealed source)
    - intracavitary
    - interstitial
    - mould
The evolution of RT techniques

- **2DRT**
- **3DRT**
- **IMRT**
- **IGRT**
- **RT+**
- **Targeted therapy**
- **Adaptive RT**

**RCT - preop vs postop RT in extremity STS**

**Study - advance RT with reduce RT volume - toxicities and local control rates**


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External beam RT

Linear accelerator (Linac)
- High energy X-ray
- 6 MV, 10 MV
15 MV
External beam RT

Goal → maximize RT dose to tumor

minimize dose to normal tissue

2D → Advanced RT techniques

3D-CRT IMRT IGRT ART

Particle beam RT

Conformal Radiotherapy (tailor-made treatment)
Advanced radiation therapy

Rationale

- Tumor dose
- OAR dose
- Target missing risk

Set up errors deletion
Organ motion reduction/compensation

OAR
CTV
ITV
SM
3D-conformal Radiotherapy (3DRT)
Intensity modulated Radiotherapy (IMRT)
Image-guided Radiotherapy (IGRT)
Adaptive RT (ART)

Tumor volumes change during preoperative RT delivery

C. Dickie et al. / Radiotherapy and Oncology 122 (2017) 458–463

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Comparison of Local Recurrence With Conventional and Intensity-Modulated Radiation Therapy for Primary Soft-Tissue Sarcomas of the Extremity

Michael R. Folkert, Samuel Singer, Murray F. Brenman, Deborah Kuk, Li-Xuan Qin, Wendy K. Kobayashi, Aimee M. Crago, and Kaled M. Alektiar

Abstract

Table 3. Grade ≥ 2 Toxicity Comparison Between Conventional RT and IMRT

<table>
<thead>
<tr>
<th>Toxity</th>
<th>Overall</th>
<th>Conventional RT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Wound complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninfected</td>
<td>28</td>
<td>8.8</td>
<td>14</td>
</tr>
<tr>
<td>Infected</td>
<td>30</td>
<td>9.4</td>
<td>13</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>127</td>
<td>39.8</td>
<td>75</td>
</tr>
<tr>
<td>Fracture</td>
<td>22</td>
<td>6.9</td>
<td>14</td>
</tr>
<tr>
<td>Nerve damage*</td>
<td>7</td>
<td>2.6</td>
<td>2</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>41</td>
<td>12.9</td>
<td>17</td>
</tr>
<tr>
<td>Edema</td>
<td>36</td>
<td>11.3</td>
<td>23</td>
</tr>
</tbody>
</table>

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Phase 2 Study of Preoperative Image-Guided Intensity-Modulated Radiation Therapy to Reduce Wound and Combined Modality Morbidities in Lower Extremity Soft Tissue Sarcoma

Brian O’Sullivan, MD\textsuperscript{1,2}; Anthony M. Griffin, MSc\textsuperscript{3}; Colleen I. Dickie, MSc\textsuperscript{1}; Michael B. Sharpe, PhD\textsuperscript{1,2}; Peter W. M. Chung, MD\textsuperscript{1,2}; Charles N. Catton, MD\textsuperscript{1,2}; Peter C. Ferguson, MD\textsuperscript{2,3}; Jay S. Wunder, MD\textsuperscript{2,3}; Benjamin M. Deheshi, MD\textsuperscript{2,3}; Lawrence M. White, MD\textsuperscript{2,4}; Rita A. Kandel, MD\textsuperscript{2,5}; David A. Jaffray, PhD\textsuperscript{1,2}; and Robert S. Bell, MD\textsuperscript{2,3}

**BACKGROUND:** This study sought to determine if preoperative image-guided intensity-modulated radiotherapy (IG-IMRT) can reduce morbidity, including wound complications, by minimizing dose to uninvolved tissues in adults with lower extremity soft tissue sarcoma. **METHODS:**

Acute wound complication
- IGRT =30.5%
- 2D-3D CRT = 43% (historical compare with NCIC)

- The need of tissue transfer, RT chronic morbidity and subsequent operation for wound complication was reduce
- Maintain local control 93.2%
 Particle Beam Radiotherapy

- Neutrons
  - Uncharged, high LET

- Protons & $\alpha$-particles
  - Charged, low LET

- Light ions e.g. carbon, neon
  - Charged, high LET

- 2 important characteristics
  - Better depth-dose distribution & reduced penumbra
    - Intensity modulated, conformal radiotherapy
  - High LET
Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas.

Yoon SS, Chen YL, Kirsch DG, Maduekwe UN, Rosenberg AE, Nielsen GP, Sahani DV, Choy E, Harmon DC, DeLaney TF.

Abstract

BACKGROUND: We sought to reduce local recurrence for retroperitoneal sarcomas by using a coordinated strategy of advanced radiation techniques and aggressive en-bloc surgical resection.

METHODS: Proton-beam radiation therapy (PBRT) and/or intensity-modulated radiation therapy (IMRT) were delivered to improve tumor target coverage and spare selected adjacent organs. Surgical resection of tumor and adjacent organs was performed to obtain a disease-free anterior margin. Intraoperative electron radiation therapy (IOERT) was delivered to any close posterior margin.

RESULTS: Twenty patients had primary tumors and eight had recurrent tumors. Tumors were large (median size 9.75 cm), primarily liposarcomas and leiomyosarcomas (71%), and were mostly of intermediate or high grade (81%). PBRT and/or IMRT were delivered to all patients, preferably preoperatively (75%), to a median dose of 50 Gy. Surgical resection included up to five adjacent organs, most commonly the colon (n = 7) and kidney (n = 7). Margins were positive for disease, usually posteriorly, in 15 patients (54%). IOERT was delivered to the posterior margin in 12 patients (43%) to a median dose of 11 Gy. Surgical complications occurred in eight patients (28.6%), and radiation-related complications occurred in four patients (14%). After a median follow-up of 33 months, only two patients (10%) with primary disease experienced local recurrence, while three patients (37.5%) with recurrent disease experienced local recurrence.

CONCLUSIONS: Aggressive resection of retroperitoneal sarcomas can achieve a disease-negative anterior margin. PBRT and/or IMRT with IOERT may possibly deliver sufficient radiation dose to the posterior margin to control microscopic residual disease. This strategy may minimize radiation-related morbidity and reduce local recurrence, especially in patients with primary disease.
Proton 3D-CRT
Intraoperative Radiotherapy (IORT)
IOERT, IOBRT
**Intraoperative Radiotherapy (IORT)**

- NCI - 35 RPS patients randomized comparing 20-Gy IORT in combination with postoperative low-dose (35- to 40-Gy) EBRT with postoperative high-dose (50- to 55-Gy) EBRT alone
  - LR was significantly lower in IORT group
  - Fewer radiation-related enteritis but radiation-related peripheral neuropathy was more frequent in IORT group

IOERT

MGH – long term results of 10-20 Gy IOERT following preoperative EBRT (45Gy) and gross tumor removal

- In IOERT group - LC = 83% and OS = 74%
- In no IOERT group - LC = 61% and OS = 30%

Brachytherapy

- Insertion of encapsulated radioisotope inside or close to tumor
- HDR Ir-192 Machine
- 2D-technique or 3D-technique
- Intracavitary, Interstitial, Surface (Mould)
- High dose to target with normal tissue protection
• MSKCC – randomized study of 164 patients
• Adjuvant brachytherapy vs surgery alone
• 10 year LC -81% in BCT and 67% in nonBCT (p=0.03) in high grade sarcoma
• The improvement in LC was limited in high grade without effect on low grade


BCT retrospective compared with IMRT in 134 high grade – 5 year LC=92% for IMRT vs 81% for BCT (p=0.04)

Alektiar KM, Brennan MF, Singer S. Local control comparison of adjuvant brachytherapy to intensity-modulated radiotherapy in primary high-grade sarcoma of the extremity. Cancer. 2011;117:3229-3234
Fractionation in Radiotherapy

• Conventional fractionation ***
  – 1.8-2 Gy/fraction, 1 fraction/day, 5 days/week

• Alter fractionation
  – Hyperfractionation
    • Smaller dose/fraction, increased number of fraction
    • Total period of time minimally changed
    • Total dose increased
  – Accelerated fractionation
    • Shortening overall treatment time
  – Hypofractionation
    • Larger dose/fraction, decreased number of fraction
Altered Fractionation

- Kosela et al
  - Preoperative hypofraction RT for extremity and trunk STS, 272 patients
  - 5 Gy × 5 Fractions and immediate surgery
  - LR = 19%, higher compared with other series


- Brant et al
  - Preoperative hyperfraction 1.2 -1.25 Gy twice daily to 50.4 Gy
  - Operations were performed 2 to 6 wks after RT.
  - LC = 91% with 16% wound complication and 7.7% bone fracture

Rationale for the use of RT

- Localized extremity soft tissue sarcoma
- Retroperitoneal sarcoma
Treatment of Localized extremity soft tissue sarcoma

- Decades ago: Amputation
- Now: Limb-sparing surgery and Radiation
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.


Abstract
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. Both randomization groups received postoperative chemotherapy with doxorubicin (maximum cumulative dose 550 mg/m²), cyclophosphamide, and high-dose methotrexate. Twenty-seven patients randomized to receive limb-sparing resection and radiotherapy, and 16 received amputation (randomization was 2:1). There were four local recurrences in the limb-sparing group and none in the amputation group (p=0.06 generalized Wilcoxon test). However, there were no differences in disease-free survival rates (71% and 78% at five years; p2 = 0.75) or overall survival rates (83% and 88% at five years; p2 = 0.99) between the limb-sparing group and the amputation treatment groups. Multivariate analysis indicated that the only correlate of local recurrence was the final margin of resection. Patients with positive margins of resection had a higher likelihood of local recurrence compared with those with negative margins (p1 less than 0.0001) even when postoperative radiotherapy was used. A simultaneous prospective randomized study of postoperative chemotherapy in 65 patients with high-grade soft-tissue sarcomas of the extremities revealed a marked advantage in patients receiving chemotherapy compared with those without chemotherapy in three-year continuous disease-free (92% vs. 60%; p1 = 0.0008) and overall survival (95% vs. 74%; p1 = 0.04). Thus limb-sparing surgery, radiation therapy, and adjuvant chemotherapy appear capable of successfully treating the great majority of adult patients with soft tissue sarcomas of the extremity.
### Need for adjuvant RT after conservative surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>LR</th>
<th>OS or DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisters et al</td>
<td>High grade (n=119) CS vs CS+Brachy RT</td>
<td>30% vs 9% (p=0.0025)</td>
<td>5 year DFS 81% vs 84% (p=0.65)</td>
</tr>
<tr>
<td>MSKCC 1996</td>
<td>Low grade (n=45) CS vs CS+Brachy RT</td>
<td>36% vs 26% (p=0.49)</td>
<td></td>
</tr>
<tr>
<td>N=164</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity, trunk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al</td>
<td>High grade (n=91) CS vs CS+EBRT *Chemo</td>
<td>20% vs 0% (p=0.001) (10 yr)</td>
<td>10 year OS 92% vs 92%</td>
</tr>
<tr>
<td>NCI 1998</td>
<td>Low grade (n=50) CS vs CS+EBRT</td>
<td>33% vs 4% (p=0.003)</td>
<td></td>
</tr>
<tr>
<td>N=141</td>
<td>Large field to 45 Gy boost to 63 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In large, deep seated, intermediated to high grade sarcoma, combination of limb sparing surgery with RT permit more conservative surgery with high local control rate ~90%
Need for RT after conservative surgery

Survival benefit for the addition of RT to surgery in ESTSs, especially for high-grade sarcoma

Purpose: The benefit of radiation therapy in extremity soft tissue sarcomas remains controversial. The purpose of this study was to determine the effect of radiation therapy on overall survival among patients with primary soft tissue sarcomas of the extremity who underwent limb-sparing surgery.

Methods and Materials: A retrospective study from the Surveillance, Epidemiology, and End Results (SEER) database that included data from January 1, 1988, to December 31, 2005. A total of 6,960 patients constituted the study population. Overall survival curves were constructed using the Kaplan-Meir method and for patients with low- and high-grade tumors. Hazard ratios were calculated based on multivariable Cox proportional hazards models.

Results: Of the cohort, 47% received radiation therapy. There was no significant difference in overall survival among patients with low-grade tumors by radiation therapy. In high-grade tumors, the 3-year overall survival was 73% in patients who received radiation therapy vs. 63% for those who did not receive radiation therapy ($p < 0.001$). On multivariate analysis, patients with high-grade tumors who received radiation therapy had an improved overall survival (hazard ratio 0.67, 95% confidence interval 0.57-0.79). In patients receiving radiation therapy, 13.5% received it in a neoadjuvant setting. The incidence of patients receiving neoadjuvant radiation did not change significantly between 1988 and 2005.

Conclusions: To our knowledge, this is the largest population-based study reported in patients undergoing limb-sparing surgery for soft tissue sarcomas of the extremities. It reports that radiation was associated with improved survival in patients with high-grade tumors. © 2010 Elsevier Inc.

Adjuvant RT in extremity soft tissue sarcoma

- In large, deep seated, intermediated to high grade sarcoma, combination of limb sparing surgery with RT permit more conservative surgery with high local control rate ~90%

- Survival benefit for the addition of RT to surgery in ESTS, especially for high-grade sarcoma
Postoperative RT in Retroperitoneal sarcoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>No. Patients</th>
<th>Local Recurrence (%)</th>
<th>Regional Recurrence (%)</th>
<th>Total Loco-Regional Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pezner et al[13]</td>
<td>Surgery+RT±IORT (57-65 Gy in 90% pts)</td>
<td>33</td>
<td>12</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>Petersen et al[9]</td>
<td>Surgery+IORT±RT</td>
<td>87</td>
<td>8</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Krempian et al[6]</td>
<td>Surgery+IORT±RT (median 60 Gy)</td>
<td>55</td>
<td>16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alektiar et al[17]</td>
<td>Surgery+IORT+RT (57-65 Gy)</td>
<td>24</td>
<td>33</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sindelar et al[18]</td>
<td>Surgery+RT+IORT (55-60 Gy)</td>
<td>15</td>
<td>—</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>Bobin et al[19]</td>
<td>Surgery+IORT+RT (57-65 Gy)</td>
<td>22</td>
<td>44</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gilbeau et al[20]</td>
<td>Surgery+RT±IORT (median 50.4 Gy)</td>
<td>45</td>
<td>—</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>Sindelar et al[18]</td>
<td>Surgery+50-55 Gy RT</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>75</td>
</tr>
<tr>
<td>Lewis et al[5]</td>
<td>Surgery+RT</td>
<td>231</td>
<td>41</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

-High rate of local relapse  
-More acute and late RT complication especially in patient with high dose RT

Pezner et al. American Journal of Clinical Oncology 2011
Lack of Survival Benefit Following Adjuvant Radiation in Patients with Retroperitoneal Sarcoma: A SEER Analysis


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Submitted for publication November 20, 2010

Background. The benefit of radiation therapy (RT) among patients with retroperitoneal sarcoma (RPS) is controversial. We performed a retrospective analysis of the effect of RT on survival among RPS patients using a nationwide cancer registry.

Methods. Utilizing data from the Surveillance, Epidemiology, and End Results (SEER) database, we identified 2308 cases of RPS from 1988 to 2004. We excluded 773 cases for age < 18, identification by autopsy only, absence of histologic confirmation, presence of metastatic disease, or lack of surgical intervention. Overall survival (OS) and disease-specific survival (DSS) were estimated using the Kaplan-Meier method. Multivariate analysis was performed using a Cox proportional hazards model, adjusting for significant covariates.

Results. Among 1535 patients who met entry criteria, RT was administered to 373 patients (24.3%). The majority of RT (n = 300, 80.4%) was administered postoperatively. Median OS was 60 and 60 mo, respectively, for patients receiving and not receiving RT (P = 0.59). Median DSS was 86 and 117 mo, respectively, for patients receiving and not receiving RT (P = 0.84). On multivariate analysis, younger age, female gender, low and intermediate histologic grade, liposarcoma histology, tumor size 5–10 cm, and completeness of resection all independently predicted better OS and DSS, while RT did not (HR for OS with RT 0.92, 95% CI 0.78–1.09 and HR for DSS with RT 0.96, 95% CI 0.78–1.17). On subgroup analysis by histology, patients with malignant fibrous histiocytoma (MFH) receiving RT demonstrated statistically improved OS (P = 0.002) and DSS (P = 0.01), respectively.

Conclusions. With the possible exception of MFH, postoperative RT offers no survival benefit in RPS. Further studies are necessary to determine if the selective application of RT is indicated.

Key Words: retroperitoneal sarcoma; radiation therapy; survival.

- Only MFH - improve OS and DSS
Surgery and Radiation Sequencing

Pre-operative RT → Surgery

OR

Surgery → Post-operative RT

Efficacy: Similar
- Excellent local control 85-100%
- Comparable overall survival
- Toxicities: Different

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## Surgery and Radiation Sequencing

<table>
<thead>
<tr>
<th>Preoperative RT</th>
<th>Postoperative RT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
</tr>
<tr>
<td>• Smaller RT fields</td>
<td>• Complete tumor specimen – pathology review for true histology and margin status</td>
</tr>
<tr>
<td>• Lower RT doses</td>
<td>• Lower risk of major wound complications</td>
</tr>
<tr>
<td>• Reduced tumor implant and seeding</td>
<td>• Larger treatment volumes</td>
</tr>
<tr>
<td>• Tumor down staging</td>
<td>• Higher doses</td>
</tr>
<tr>
<td>• Radiobiological advantage</td>
<td>• More hypoxic tissue</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Radiobiology disadvantage</strong></td>
</tr>
<tr>
<td>• High risk of major wound complications</td>
<td>• High incidence of late toxicity</td>
</tr>
</tbody>
</table>
Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial.


Closed early after a planned, preliminary analysis showed a significant difference in primary outcome (wound complication).

METHODS: After stratification by tumour size (< or = 10 cm or >10 cm), we randomly allocated 94 patients to preoperative radiotherapy (50 Gy in 25 fractions) and 96 to postoperative radiotherapy (66 Gy in 33 fractions). The primary endpoint was rate of wound complications within 120 days of surgery. Analyses were per protocol for primary outcomes and by intention to treat for secondary outcomes.

FINDINGS: Median follow-up was 3.3 years (range 0.27-5.6). Four patients, all in the preoperative group, did not undergo protocol surgery and were not evaluable for the primary outcome. Of those patients who were eligible and evaluable, wound complications were recorded in 31 (35%) of 88 in the preoperative group and 16 (17%) of 94 in the postoperative group (difference 18% [95% CI 5-30], p=0.01). Tumour size and anatomical site were also significant risk factors in multivariate analysis. Overall survival was slightly better in patients who had preoperative radiotherapy than in those who had postoperative treatment (p=0.0481).

INTERPRETATION: Because preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy, the choice of regimen for patients with soft-tissue sarcoma should take into account the timing of surgery and radiotherapy, and the size and anatomical site of the lesion.
Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma.


<table>
<thead>
<tr>
<th>Grade &gt; 2</th>
<th>Pre-Op</th>
<th>Post-Op</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>31.5%</td>
<td>48.2%</td>
<td>0.07</td>
</tr>
<tr>
<td>Edema</td>
<td>15.1%</td>
<td>23.2%</td>
<td>ns</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>17.8%</td>
<td>23.2%</td>
<td></td>
</tr>
</tbody>
</table>

using the Fisher's exact test. Function scores by toxicity were analyzed using the Wilcoxon rank sum test.

Multivariate logistic regression was used to evaluate the joint effect of treatment arm, field size, and dose on subcutaneous tissue fibrosis, joint stiffness and edema.

RESULTS: 27 of 56 patients (48.2%) in the postoperative arm compared to 23 of 73 (31.5%) in the preoperative arm had grade 2 or greater fibrosis (P = 0.07). Although not statistically significant, edema was more frequent in the postoperative arm, 13 of 56 (23.2%) versus 11 of 73 (15.5%) in the preoperative arm, as was joint stiffness, 13 of 56 (23.2%) versus 13 of 73 (17.8%). Patients with significant fibrosis, joint stiffness or edema had significantly lower function scores on both measures (all P-values < 0.01). Field size was predictive of greater rates of fibrosis (P = 0.002) and joint stiffness (P = 0.006) and marginally predictive of edema (P = 0.06).

CONCLUSIONS: Patients treated with postoperative radiotherapy tended to have greater fibrosis. Fibrosis, joint stiffness and edema adversely affect patient function.
Factors predict late RT toxicity

- Field size  
- Dose of RT  

Larger and higher in post-op RT
Phase I – Dose 45-50.4 Gy, 1.8-2 Gy once daily fraction

**GTV** - the resected “GTV” recreated form pre-op imaging

**Elective CTV** - consider compartment at risk of microscopic spread. Should include biopsy site, drain site and scar

GTV+ 4 cm longitudinal, 1.5 cm radially

**Elective PTV = CTV+ 1 cm in all direction (vary by institutional protocol)**

Phase II – Dose 10-16 Gy, total dose of 60-66 Gy

- **Boost CTV**: GTV + 2cm longitudinal, 1.5 cm radial
- **Boost PTV**: boost CTV+ 1 cm in all direction (vary by institutional protocol)

Strip of tissue should be spared laterally (if possible): to decrease the risk of lymphedema
Target definition for postop RT - phase I

Target definition for postop RT - phase II

Base on RTOG sarcoma working group consensus (2011)

**GTV:** Delineated by T1 post gad MRI

**CTV:** for intermediate to high grade sarcoma $\geq 5$ cm

  GTV + 4 cm in the longitudinal and 1.5 cm radially, not need to be expanded beyond the compartment or surface of bones and fascia

  Peritumoral edema on T2 MRI should included within CTV

  Extensive T2 edema – may be excluded clinical judgment suggest the risk of the edema harboring sarcoma beyond GTV is low or cause excessive toxicity

**PTV:** CTV + 0.5 cm to 1 cm margin (depend on institute protocol)

A total dose of 50 Gy in 25 fraction with surgery following 4-8 weeks later
Fig. 1. Schematic descriptions of target definitions for preoperative radiotherapy (RT). (A) Patient to be treated with preoperative RT. Sarcoma delineated using T1-weighted, postgadolinium magnetic resonance imaging (MRI) scan fused to planning computed tomography (CT) scan. This gross tumor volume (GTV) does not include peritumoral edema, generally best seen on T2-weighted MRI scan. (B) GTV transversely expanded with 1.5 cm but constrained at surfaces of fascia and bone, unless

Fig. 1. Example of individual and consensus (red) contours of gross tumor volume on axial computed tomography for patient with large high-grade sarcoma of distal aspect of right thigh.

Fig. 2. Example of individual and consensus (red) contours of clinical target volume on axial computed tomography for patient with large high-grade sarcoma of distal aspect of right thigh.
Finding sarcoma cells 4 cm beyond the tumor gives a basis for 4 cm longitudinal expansion of the GTV to CTV.

Are large CTV expansion necessary?

2 prospective trials are addressing this issue

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

- **RTOG 0630**: A phase II trial of image guide preoperative radiotherapy for primary soft tissue sarcomas of the extremity
VORTEX trial to assess if a reduced volume of post-operative radiotherapy increases limb function without compromising local control.

**Trial Schema**

- Biopsy
  - Assessment of extent of tumour by imaging
  - *Patient registration and completion of pre-operative TESS questionnaire
  - Wide local excision of sarcoma
  - Wound healing and assessment
  - Oncology appointment post-operation

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

- Radiotherapy planning

**Control Arm**
- Conventional two-phase treatment
  - Total dose: 66Gy in 33#
  - Weeks 1-5: 2Gy x 5 days Weekly
  - Week 6: 2Gy x 5 days
  - Week 7: 2Gy x 3 days

**Research Arm**
- Single-phase treatment to CTV2 only
  - Total dose: 66Gy in 33#
  - Weeks 1-6: 2Gy x 5 days Weekly
  - Week 7: 2Gy x 3 days

- CTV1: 5cm margin to GTV or 1cm to the scar, whichever is longer in the cranio-caudal direction and minimum margin of 2cm axially
- CTV2: 2cm cranio-caudal margin to GTV and minimum margin of 2cm axially

*Cancer Research UK*

Completed accrual and await for the results.
RTOG 0630 Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity

**SCHEMA**

<table>
<thead>
<tr>
<th>Preoperative IGRT (3D-CRT or IMRT)</th>
<th>Postoperative Radiotherapy Boost For patients with positive margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients:</td>
<td></td>
</tr>
<tr>
<td>R Cohort A (Closed 1/8/10)</td>
<td>External beam RT</td>
</tr>
<tr>
<td>E Patients receiving neoadjuvant or adjuvant</td>
<td>2 weeks post-surgery</td>
</tr>
<tr>
<td>G chemotherapy or both = <strong>50 Gy in 25 daily fractions</strong></td>
<td>Surgery</td>
</tr>
<tr>
<td>I OR 4-8 weeks</td>
<td>16 Gy in 8 daily fractions</td>
</tr>
<tr>
<td>S Patients receiving concurrent or interdigitated chemotherapy = <strong>44 Gy in 22 daily fractions</strong></td>
<td>OR</td>
</tr>
<tr>
<td>T preoperative completion of OR Brachytherapy</td>
<td>5 days post-surgery</td>
</tr>
<tr>
<td>E RT (and chemo if given) OR HDR = 3.4 Gy/fraction in 4 fractions with at least 6 hours between fractions</td>
<td>HDR = 3.4 Gy/fraction in 4 fractions with at least 6 hours between fractions</td>
</tr>
<tr>
<td>R Cohort B Cohort B Patients not receiving chemotherapy = <strong>50 Gy in 25 daily fractions</strong></td>
<td>Intraoperative RT</td>
</tr>
<tr>
<td></td>
<td>10-12.5 Gy in a single fraction</td>
</tr>
</tbody>
</table>
RTOG 0630- CTV margins

CTV for intermediate to high grade tumor \( \geq 8 \) cm:

CTV = GTV and suspicious edema plus 3 cm margins in the longitudinal (proximal and distal) directions.

If this causes the field to extend beyond the compartment, the field can be shortened to include the end of a compartment.

The radial margin from the lesion should be 1.5 cm included any portion of the tumor not confined by an intact fascial barrier or bone or skin surface.
RTOG 0630- CTV margins

CTV for all other tumors

CTV= GTV and suspicious edema (defined by MRT T2 images) plus 2 cm margins in the longitudinal (proximal and distal) directions

If this causes the field to extend beyond the compartment, the field can be shorted to include the end of a compartment

The radial margin from the lesion should be 1 cm included any portion of the tumor not confined by an intact fascial barrier or bone or skin surface
Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial

Dian Wang, Qiang Zhang, Burton L. Eisenberg, John M. Kane, X. Allen Li, David Lucas, Ivy A. Petersen, Thomas F. DeLaney, Carolyn R. Freeman, Steven E. Finkelstein, Ying J. Hitchcock, Manpreet Bedi, Anurag K. Singh, George Dundas, and David G. Kirsch

Late RT toxicities (>= grade 2)
- IGRT = 10.5%
- 2D-3D CRT = 37% (historical compare with NCIC)
A diagram showing the failure rates over time for different types of failures:

- **Distant failure**: 37.3% at 2 years.
- **Local failure**: 11.4% at 2 years.
- **Second primary**: 5.1% at 2 years.
- **Regional failure**: 0% at 2 years.

The no. at risk for each category over time:

- **Distant**: 79, 51, 46, 37, 14
- **Local**: 79, 64, 56, 46, 15
- **SPT**: 79, 66, 57, 43, 14
- **Regional**: 79, 69, 60, 49, 15

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2 year OS = 80.6%
**Table 4. Treatment Parameters for Five In-Field Local Recurrences**

<table>
<thead>
<tr>
<th>Tumor Size (cm)</th>
<th>Histologic Grade</th>
<th>Histology</th>
<th>Resection Status</th>
<th>Postoperative Radiation Boost</th>
<th>Target Volume</th>
<th>Target Volume Dose Volume Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7</td>
<td>3</td>
<td>Leiomyosarcoma</td>
<td>0</td>
<td>No</td>
<td>Acceptable variation</td>
<td>Per protocol</td>
</tr>
<tr>
<td>6.1</td>
<td>3</td>
<td>Malignant peripheral nerve sheath tumor, spindle cell</td>
<td>1</td>
<td>No</td>
<td>Acceptable variation</td>
<td>Unacceptable variation</td>
</tr>
<tr>
<td>7.2</td>
<td>3</td>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>1</td>
<td>Yes</td>
<td>Per protocol</td>
<td>Per protocol</td>
</tr>
<tr>
<td>12.0</td>
<td>3</td>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>1</td>
<td>Yes</td>
<td>Unacceptable variation</td>
<td>Unacceptable variation</td>
</tr>
<tr>
<td>16.5</td>
<td>3</td>
<td>Pleomorphic leiomyosarcoma</td>
<td>0</td>
<td>No</td>
<td>Per protocol</td>
<td>Per protocol</td>
</tr>
</tbody>
</table>

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RT boost is needed following preop RT and surgery with positive resection margin?

Methods to add postop RT boost
- EBRT – 16 Gy/8 fractions
  - Start 2 week post surgery
  - Metallic clips – recommend to define the residual tumor bed for a positive margin
- Brachytherpay (LDR or HDR)
  - Not start until day 5 after surgery and must completed within 2 week after surgery.
- IORT 10-12.5 Gy
RT boost is needed following preop RT and surgery with positive resection margin?

- 216 ESTS patients with a positive surgical margin
- 52 - preoperative RT alone (50 Gy)
- 41 - preoperative RT + a postoperative boost (16 Gy, a total of 66 Gy)
- LR – preop RT alone - 6 of 52
- boost group - 9 of 41
- Five-year estimated LR-free survivals were 90.4% and 73.8%, respectively (p = 0.13)

The results - not identify a LC advantage for an RT boost

67 patients - pre-operative RT and surgery with positive margin(s).
- No RT boost = 10
- BRT or IORT boost = 10
- EBRT boost = 47
- 5 year LC for no boost, BRT/IORT boost, and EBRT boost were 100%, 78%, and 71% (P = 0.5).
Favorable anatomical issues, including the tumor displacement of critical radiosensitive organs away from the preoperative RT field, thereby reducing toxicity and improving tolerance.
Phase II trial

Combined management of retroperitoneal sarcoma with dose intensification radiotherapy and resection: Long-term results of a prospective trial

Myles J.F. Smith a,b, Paul F. Ridgway c, Charles N. Catton a,d, Amanda J. Cannell a,b, Brian O’Sullivan a,d, Lynn A. Mikula e, Julia J. Jones f, Carol J. Swallow a,b,*

a The University of Toronto Sarcoma Group, Princess Margaret Hospital and Mount Sinai Hospital; b Department of Surgery, University of Toronto, Canada; c Department of Surgery, Adelaide and Meath Hospital, Dublin 24, Ireland; d Department of Radiation Oncology, University of Toronto; e The Peterborough Clinic, Peterborough; and f The R. S. McLaughlin Durham Regional Cancer Centre, Oshawa, Canada

ABSTRACT

Background: Late failure is a challenging problem following resection of retroperitoneal sarcoma (RPS). We investigated the effects of preoperative XRT plus dose escalation with early postoperative brachytherapy (BT) on long-term survival and recurrence in RPS.

Methods: From June 1996 to October 2000, eligible patients with resectable RPS were entered onto a phase II trial of preoperative XRT (45–50 Gray) plus postoperative BT (20–25 Gray). Kaplan Meier survival curves were constructed and compared by log rank analysis (SPSS 21.0).

Results: All 40 patients had preoperative XRT and total gross resection as part of the prospective trial, nineteen received BT (48%). Median follow-up was 106 months. For the entire cohort, OS at 5 and 10 years was 70% and 64% respectively; RFS at 5 and 10 years was 69% and 63%. RFS was significantly reduced in high versus low grade RPS at 5 years (53% vs. 88%, p = 0.016), but not at 10 years (53% vs. 75%, p = 0.079). RFS and OS at 10 years were reduced in patients who presented with recurrent compared to primary disease (RFS 30% vs. 74%, p = 0.015; OS 36% vs. 76%, p = 0.036). At 10 years, neither RFS nor OS was improved in patients who received BT compared to those who did not (RFS 56% vs. 65%, p = 0.54; OS 52% vs. 76%, p = 0.23).

Conclusions: In this prospective trial with mature follow-up, long-term OS and RFS in patients who underwent combined preoperative XRT plus resection of RPS compare favourably with those reported in retrospective institutional and population-based series. Postoperative BT was associated with unacceptable toxicity and did not contribute to disease control.

Condensed abstract: In a prospective trial with mature follow-up, preoperative radiation combined with complete resection of retroperitoneal sarcoma resulted in favourable long-term RFS and OS compared to historical controls. Dose escalation with postoperative brachytherapy was not associated with better disease control.

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Contouring

1. GTV

2. Contour the entire “bowel bag” or peritoneal cavity using guidelines from RTOG atlas on the RTOG website

3. CTV - uniform GTV expansion of 1.5 cm with edited reduction at bone (0 mm), bowel bag, and air cavity (5 mm), renal and hepatic interfaces (2 mm), and skin surface (3 mm)

4. The high-risk boost - high risk for positive margins following resection. Areas of tumor located along posterior abdominal wall, ipsilateral para- and prevertebral space, major vessels, or organs that the surgeon would leave in situ.

5. Contour small bowel, colon, stomach, and duodenum.
De-differentiate liposarcoma

Colors correspond to the contours:
Red=gross tumor volume; blue=clinical target volume; yellow=high-risk clinical target volume boost; pink=stomach; light blue = duodenum; mustard yellow = small bowel; brown = colon; and green = bowel bag.

EORTC study

- Arm I: En-bloc resection
- Arm II: preoperative RT followed by en-bloc resection 3D-CRT or IMRT 50.4 Gy/28 fractions.
- 256 pt – closed to accrual
- Primary objective: abdominal recurrence free survival
RT simulation and treatment planning process
Positioning and Simulation

Positioning:

• Depends on the site of the primary lesion
• Stable and reproducible position – basic essential
• Make custom immobilization device to reproduce position on a daily RT treatment
• Optimal positioning to treat the affected compartment with minimal treatment of uninvolved tissue
• Obtain CT or MRI scan in treatment position
CT simulator  MRI simulator
Immobilization device

Optimal positioning to treat the affected compartment with minimal treatment of uninvolved tissue
Target delineation and treatment planning
Target delineation and treatment planning

A

B

C

D

ID: Motorized (35 deg)

96.2 Gy
/33fr.

59.2 Gy
/33fr.

Tumor

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Acute RT skin reaction

Preoperative RT - 25% to 46%
Postoperative RT - 6% to 29%
- Usually reversible

Dry desquamation

Hyperpigment

Moist desquamation
Fatal RT complication

- Duodenocaval fistula (DCF)
- Rare but severe and fatal
- The mortality rate -> 40%.
- The most common etiology
  - Trauma
  - Resection of a retroperitoneal tumor combined with adjuvant postoperative irradiation
Late RT Toxicities

– Edema, subcutaneous fibrosis, decreased muscle strength, decreased range of motion, pain, and, less commonly, bone fracture and peripheral nerve damage

– Higher complication rates with higher doses (>60-63 Gy) and larger field sizes: post-op RT

– Large RT field sizes have also been associated with more edema, fibrosis, and joint stiffness
Conclusions

• The local recurrence of ESTS following limb-sparing surgery alone 30-50%
• The additional of pre-or postoperative RT improves local control to 80-90% with excellent functional outcome
• For RPS, the benefit of RT has not been proven
  • Preoperative RT seems to be the safest process of delivery
• The advance RT techniques with the reduction in the volumes of RT give an advantage of adequate tumor dosage with less toxicity
Conclusions

• Most evidence
  – No level 1 evidence, no well design RCT
• Relative small number of patient
• Short F/U - advanced RT technique
• Disagreement exists across the published series
• Benefit – Increase local control, low toxicity
  - No overall survival benefit
Indication for RT

- All deep seated tumors
- All high grade tumors
- Intermediate grade tumor, size >5 cm
- Low grade tumors:
  - Positive or close ( <1 cm ) resection margins
  - Locally recurrent disease following initial wide excision
  - Tumor location that would not be ameable to subsequent salvage surgery
• **Postoperative therapy:**
  – Initial volume usually 45 Gy
  – Final cone down to 63-65 Gy
  – 1.8 Gy fractions, five fractions per week

• **Preoperative irradiation:**
  – Single phase treatment with RT dose of 45 to 55.8 Gy, conventional fraction
  – Intraoperative boost or additional postoperative irradiation as indicated by surgical margin (optional)
Volume of RT

- Preoperative RT

Smaller volume
Tumor + margins

Postoperative RT

Larger RT volume
Entired operative bed + margins
Pre-operative RT

Lower dose
50 Gy / 25 fractions

Smaller RT volume
Tumor + margins

More acute wound complication (35% vs 17%)

Usually reversible

Post-operative RT

Higher dose
60 Gy/30 fractions

Larger RT volume
Entire operative bed + margins

More late complication (fibrosis, edema, joint stiffness)

Usually irreversible
Surgery and Radiation sequencing

- Equivalent efficacy
- Different toxicities
- Treatment approach should be individualized

We (Radiation oncologist) prefer pre-op RT for most situations

- Lower dose, small treatment volume, less irreversible long term toxicity