Postoperative intensity-modulated radiation therapy provides favorable local control and low toxicities in patients with soft tissue sarcomas in the extremities and trunk wall

Jianyang Wang
Shuilian Wang
Yongwen Song
Xinfan Liu
Jing Jin
Weihu Wang
Zihao Yu
Yueping Liu
Yexiong Li

Department of Radiation Oncology, Cancer Hospital and Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People’s Republic of China

Purpose: To investigate the efficacy and toxicity of postoperative intensity-modulated radiation therapy (IMRT) for patients with soft tissue sarcomas (STSs) in the extremities and trunk wall.

Patients and methods: Eighty patients with localized STSs in the extremities and trunk wall treated with function-conserving surgery and postoperative IMRT were analyzed. The primary locations were in the extremities in 51 patients and in the trunk wall in 29 patients. The margins were positive in nine patients and negative in 71 patients. The median dose of IMRT was 64 Gy.

Results: At a median follow-up time of 38 months, eight patients developed local recurrences. The 5-year local control (LC) rate was 88.1%. The patients with negative margins exhibited much better LC than did those with positive margins (90% vs 64.8%, \( P = 0.023 \)). Multivariate analysis revealed that positive margin was an independent risk factor for LC. The 5-year distant metastasis-free survival, disease-free survival, and overall survival rates were 75.2%, 72.6%, and 83.6%, respectively. Large tumor size (>5 cm) was significantly associated with poor overall survival. Edema and joint stiffness were observed in 17.6% and 9.8% of patients with extremity STSs, respectively.

Conclusion: IMRT provides excellent LC and low toxicity for patients with STSs in the extremities and trunk wall.

Keywords: soft tissue sarcoma, extremities and trunk wall, intensity-modulated radiation therapy, local control, toxicities

Introduction
In the past 30 years, the management of soft tissue sarcoma (STS) had evolved from amputation and similar radical resection approaches to more conservative, function-preserving surgeries combined with radiotherapy (RT). Evidence from two randomized trials demonstrated that RT in combination with limb-sparing surgery achieves local control (LC) and overall survival (OS) rates that are comparable to those of amputation.\(^{1,2}\) In both of these trials, conventional two-dimensional (2D) external beam RT or brachytherapy technique was used.

Standard of practice of STS has changed to intensity-modulated radiation therapy (IMRT) within the past decade, as two dosimetric studies revealed that IMRT has the advantage of improving the dose distribution to large tumor targets while sparing the normal tissue in STSs in the thigh.\(^{3,4}\) Although various studies have demonstrated...
the improved survival and decreased toxicity that are associated with the use of IMRT in the treatment of other malignant tumors. Some previous studies have reported on the favorable outcomes achieved with IMRT for pediatric and adult patients with STS. Thus, whether IMRT can be as effective in the treatment of STS patients like 2D-RT without posing risks to LC remains an important issue. In this large series of patients with STSs in the extremities and trunk wall, we evaluated the outcomes and toxicities of adjuvant IMRT following function-preserving surgery.

Patients and methods

Patients

This study was approved by the Institutional Ethic Committee of Cancer Hospital & Institute, Chinese Academy of Medical Sciences (CAMS) in October 2012. As the study was a retrospective study, there was no intervention regarding the patients and their treatment. Only the clinical data were reviewed, and patient confidentiality was upheld. Therefore, written patient consent was deemed unnecessary. The patients with STS treated with function-preserving surgery and RT in our institution between July 2005 and November 2011 were identified. Eighty patients who met the following criteria were included in this study: tumor located in the extremities or trunk wall, treated with postoperative IMRT, no distant metastasis, and no previous RT. The patients were staged according to the Seventh American Joint Committee on Cancer staging system.

Surgery and IMRT

All patients received wide local excisions. The majority of patients (n=71, 88.8%) underwent R0 resections (>1 mm margin), and nine patients received R1 (≤1 mm margin or microscopic residual disease) or R2 (gross residual disease) resection.

RT was administered 4–6 weeks after surgery. The patients were immobilized with a board-fixed shoe in T-shape shoe and vacuum cushion for patients with tumors in extremities or trunk wall, treated with postoperative IMRT, no distant metastasis, and no previous RT. The patients were staged according to the Seventh American Joint Committee on Cancer staging system.

Follow-up, end points, and statistics

The follow-up schedule consisted of clinical evaluations that included toxicity assessments every 3 months for the first 2 years and imaging of the primary lesion site and chest every 6 months. These examinations were subsequently repeated every 6 months for 3 years and yearly thereafter.

The OS, disease-free survival (DFS), LC, and distant metastasis-free survival (DMFS) were calculated from the date of surgery. Local recurrence was defined as any recurrence in the field; no beams entering or exiting through contralateral bone; no beams entering or exiting through contralateral leg if possible; no hot spots (≥107% of the prescribed dose) are allowed to be located on the bone.

Results

Clinical characteristics

Table 1 summarizes the patient characteristics. The most common histologies were malignant fibrous histiocytomas (23.8%, n=19) and liposarcomas (23.8%, n=19), followed by fibrosarcomas (15.0%, n=12) and synovial sarcomas (15.0%, n=12). The median age was 50 years (range: 5–74).
Local control
Among the 80 patients, eight patients developed local recurrence with (n=2) or without (n=6) distant metastasis. The actual 3-year LC rate was 92.9%, and the estimated 5-year LC rate was 88.1% for all patients (Figure 1).
Incomplete resection and male sex were associated with local recurrence (Table 2). Patient with positive margins exhibited significantly more local recurrence than did those with negative margins. The 5-year LC rates were 90% for the patients with negative margins (R0 resection) and 64.8% for those with positive margins (R1 + R2 resection, P=0.023).
The 5-year LC rates were 100% for women and 80.0% for men (P=0.032). Multivariate analysis revealed that only positive margin (hazard ratio 5.33, 95% confidence interval 1.19–23.86, P=0.029) exerted an independent adverse influence on LC.

Survival
Twelve patients died due to their diseases. At a median follow-up time of 38 months for the surviving patients, the actual 3-year OS, DFS, and DMFS rates were 87.4%, 77.3%, and 81.2%, respectively. The estimated 5-year OS, DFS, and DMFS rates were 83.6%, 72.6%, and 75.2%, respectively (Figure 1). The patient characteristics were evaluated for prognostic significance for OS (Table 2). Large tumor size was associated with poor OS. The 5-year OS rates were 68.9% for the patients with tumors larger than 5 cm and 94.7% for those with tumors of 5 cm or less (P=0.041). No factors were found to be related to OS in the multivariate analysis.

Morbidity
The late complications are shown in Table 3. Among the 51 patients with extremity STSs, nine (17.6%) had grade 1–4
Table 3 Late postoperative morbidities of IMRT in 51 patients with soft tissue sarcomas in the extremities

<table>
<thead>
<tr>
<th>Late radiation morbidity</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Joint stiffness (≥ CTCAE grade 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Abbreviations: IMRT, intensity-modulated radiation therapy; CTCAE, Common Terminology Criteria for Adverse Events.

edema, and five (9.8%) had grades 1–3 joint stiffness. Only one patient developed grade 3 joint stiffness. This patient presented with recurrent bulky disease localized in his hip joint was covered with CTV at a total dose of 50 Gy. Another patient developed grade 3 acute dermatitis and a wound complication, and he lived with a chronic nonhealing ulcer. Other severe late toxicities, such as bone fracture and secondary neoplasm, did not occur in any patients.

Discussion
To our knowledge, our study represents one of the largest studies of IMRT for the postoperative treatment of STS in the modern era. IMRT produced favorable LC and OS among patients with STSs in the extremities and trunk wall. Positive margin independently and adversely influenced LC in the multivariate analysis. Furthermore, the late morbidity of IMRT was low compared with those reported in previous studies that have utilized 2D radiation techniques.13–15

The clinical importance of adjuvant IMRT for STS is not well defined.8–10 One large study from the Memorial Sloan-Kettering Cancer Center reported favorable prognoses following preoperative and postoperative IMRT in 41 adult patients with extremity STSs. The 5-year LC and OS rates for these patients were 94% and 64%, respectively (median follow-up time, 35 months).8 Similarly, the treatment outcomes following postoperative IMRT in patients with STSs in the extremities and trunk wall were excellent in this series. The 5-year LC rates in this series were 88.1% for all patients and 91.0% for the patients with extremity STSs, and the 5-year OS rate was 83.6%. The high OS rate observed in the study can be partially explained by the low proportions of large-sized and high-grade tumors.8 Furthermore, the LC and OS in this series were similar to those reported in other studies that utilized conventional radiation techniques.2,16,17 Consistent with previous studies of conventional RT,18–23 our study clearly demonstrated that patients with positive margins exhibited significantly more local recurrence that did those with negative margins in both the univariate and the multivariate analyses. This finding indicates that IMRT might not compensate for poor surgeries with positive margins. In contrast, two other studies of the use of IMRT for extremity STSs achieved excellent LCs for both patients with negative and positive margins.8,24

The possible advantage of IMRT in the treatment of STS is the reduction in late toxicities.25 Compared with conventional RT and 3D conformal RT, IMRT provides homogeneous CTV coverage and greater sparing of the surrounding normal tissues.3,4,26 Compared with the early studies of conventional RT,8,13–15,27 the postoperative IMRT in the current study resulted in acceptably lower rates of late complications, including a 17.7% rate of edema and a 9.8% rate of joint stiffness. Severe late complications were rare, and no patient experienced bone fracture. In contrast, Davis et al reported that 23.3% of patients experienced edema and 23.3% had joint stiffness following treatment with 2D-RT.15 Cannon et al showed that the 20-year chronic radiation-related rate of limb complications was 13% in patients with primary lower extremity STSs.27 The reported overall fracture rates range from 1.2% to 6.3%.8,13,14,27

This study is limited by its retrospective nature. Prospective assessment of the functional outcomes was not possible, which might have introduced bias into the results. Additionally, because the median follow-up time was relatively short, the long-term complications of IMRT for STS need further evaluation.

Conclusion
Postoperative IMRT provides excellent LC and low late morbidity rates in patients with STSs in the extremities and trunk wall. These findings clearly indicate the feasibility and efficiency of IMRT in clinical practice. As observed in previous studies of the use of IMRT for other malignancies,5,6 the precise dose distributions achieved with IMRT in the treatment of STS produced favorable outcomes by sparing the surrounding normal tissues.

Acknowledgment
The article was accepted as an oral presentation at the 55th Annual Meeting of ASTRO on September 24, 2013, in Atlanta, USA.

Disclosure
The authors report no conflicts of interest in this work.
References


