High Dose Rate Interstitial Brachytherapy in Soft Tissue Sarcoma: Technical Aspects and Results

Mison Chun¹, Seunghee Kang¹, Byoung-Suck Kim² and Young-Taek Oh¹

¹Department of Radiation Oncology and ²Department of Orthopedic Surgery, School of Medicine, Ajou University, Suwon, Korea

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Background: Radiation is essential for function preservation in the management of soft tissue sarcoma (STS). One of the advantages of brachytherapy is that it allows for specific localization of radiation dose to the tumor bed. We examined the results of our clinical experiences with immediate postoperative high dose rate (HDR) brachytherapy and external beam radiation treatment (EBRT) for STS.

Methods: A total of 17 patients (11 primary and six recurrent) between 1995 and 1999 were included in this review. The inclusion criteria for HDR and EBRT were as follows: (1) high-grade tumor, (2) low-grade tumor of ≥10 cm, (3) recurrent tumor, (4) tumor abutting or invading critical structures and (5) positive margin. The catheters (six French) were placed parallel to the long axis of the tumor with a 1–1.5 cm spacing in between. If necessary, muscle or gel-foam was placed over the critical structures to maintain a minimum space of 0.5 cm from the catheters. On postoperative day 6, patients received HDR (2–3 Gy/fraction ×6, twice daily). Three weeks later, patients received EBRT (total 36–60 Gy). The follow-up duration was between 13 and 60 months (median 31 months).

Results: There was no local failure within the radiation field in any of the patients. One patient required wound revision for delayed healing after brachytherapy. During EBRT, most patients experienced only mild erythema (grade 1 or 2 skin reaction). In long-term follow-up, there were no patients with neuropathy or significant fibrosis.

Conclusions: Our results suggest that immediate postoperative HDR with a total dose of 12–18 Gy over 3 days is an effective treatment combined with EBRT in the management of STS.

Key words: high dose rate – brachytherapy – radiation therapy – soft tissue sarcoma

INTRODUCTION

Radiotherapy is an integral part of function-preserving treatment in soft tissue sarcoma (STS). Both pre- and postoperative external beam treatments with limited surgery are known to be equally effective in reducing the local recurrence rate. Also, many reports have confirmed the effectiveness of interstitial brachytherapy either alone or combined with external beam radiation therapy (EBRT) in the management of STS (1–6). The advantages of brachytherapy include (1) reduction of treatment time, (2) high radiation dose to the immediate tumor bed, (3) more effective delivery of radiation (less hypoxic and higher biological dose) and (4) relative sparing of overlying skin and surrounding normal tissue. Most reports have described the results including techniques with low dose rate (LDR) brachytherapy, but there are limited data available on high dose rate (HDR) brachytherapy (7–10).

This paper presents a retrospective review of clinical experiences with HDR brachytherapy for the management of either primary or recurrent STSs.

PATIENTS AND METHODS

PATIENTS’ CHARACTERISTICS (TABLE 1)

There were 17 patients with STS who completed both immediate postoperative interstitial HDR brachytherapy and EBRT between May 1995 and June 1999. The selection criteria for HDR brachytherapy in our institution were as follows: (1)
high-grade sarcoma, (2) low-grade tumor of ≥10 cm in diameter, (3) locally recurrent tumor, (4) tumor abutting or invading major neurovascular or skeletal structures of the limb and (5) tumor with positive margin after limited surgery whose location was difficult to obtain. Among the nine patients who underwent the limited surgery close, microscopic and gross positive margins were noted in two, six and one patients, respectively. They had either primary (in 11 patients) or recurrent sarcoma (in six patients). Two recurrent cases had received previous EBRT (disease-free interval of 3 and 4 years).

A total of five patients received adriamycin-containing adjuvant chemotherapy after completion of EBRT.

TECHNIQUES
All patients consulted a radiation oncologist prior to the surgical procedure and discussed the role of brachytherapy and the

### Table 1. Patients’ characteristics and treatment results

<table>
<thead>
<tr>
<th>No.</th>
<th>Pathology</th>
<th>Site</th>
<th>Tumor size (cm)</th>
<th>Resection margin</th>
<th>Dose (Gy)</th>
<th>Prescription point (cm)</th>
<th>No. of catheters</th>
<th>Complication</th>
<th>Follow-up status</th>
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<tr>
<td>(1) Primary cases:</td>
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<tr>
<td>1</td>
<td>MPNST&lt;sup&gt;a&lt;/sup&gt; High grade</td>
<td>Thigh</td>
<td>15 × 7</td>
<td>(–)</td>
<td>2.5 ×4</td>
<td>1</td>
<td>2</td>
<td>(–)</td>
<td>55.8 (–)</td>
</tr>
<tr>
<td>2</td>
<td>Myxoid liposarcoma</td>
<td>Thigh</td>
<td>7 × 4</td>
<td>Micro (+)</td>
<td>2 ×6</td>
<td>0.7</td>
<td>5</td>
<td>100</td>
<td>55.8 (–)</td>
</tr>
<tr>
<td>3</td>
<td>Fibrosarcoma High grade</td>
<td>Arm</td>
<td>3.5 × 3.5</td>
<td>Micro (+)</td>
<td>2 ×6</td>
<td>0.75</td>
<td>3</td>
<td>(–)</td>
<td>55.8 (–)</td>
</tr>
<tr>
<td>4</td>
<td>Rhabdomyosarcoma</td>
<td>Arm</td>
<td>1.7 × 1.5</td>
<td>(–)</td>
<td>2 ×6</td>
<td>0.5</td>
<td>3</td>
<td>28</td>
<td>50 (–)</td>
</tr>
<tr>
<td>5</td>
<td>Leiomyosarcoma High grade</td>
<td>Leg</td>
<td>9 × 5</td>
<td>Close</td>
<td>2.5 ×6</td>
<td>1</td>
<td>4</td>
<td>51</td>
<td>54 (–)</td>
</tr>
<tr>
<td>6</td>
<td>MFH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Shoulder</td>
<td>2 × 3</td>
<td>Micro (+)</td>
<td>2.5 ×6</td>
<td>1</td>
<td>5</td>
<td>(–)</td>
<td>52.9 (–)</td>
</tr>
<tr>
<td>7</td>
<td>Well differentiated liposarcoma</td>
<td>Buttock</td>
<td>16 × 12</td>
<td>Micro (+)</td>
<td>2.5 ×6</td>
<td>1</td>
<td>4</td>
<td>(–)</td>
<td>54 (–)</td>
</tr>
<tr>
<td>8</td>
<td>Well differentiated liposarcoma</td>
<td>Buttock</td>
<td>13 × 7</td>
<td>(–)</td>
<td>2.5 ×1 → 3 ×5</td>
<td>1 → 0.7</td>
<td>3</td>
<td>113 → 56–93</td>
<td>54.4 Skin graft due to delayed wound healing after EBRT</td>
</tr>
<tr>
<td>9</td>
<td>Leiomyosarcoma High grade</td>
<td>Arm</td>
<td>6 × 4</td>
<td>(–)</td>
<td>3 ×6</td>
<td>0.7</td>
<td>2</td>
<td>25</td>
<td>50.4 (–)</td>
</tr>
<tr>
<td>10</td>
<td>Well differentiated liposarcoma</td>
<td>Shoulder</td>
<td>12 × 10</td>
<td>Close</td>
<td>2.5 ×6</td>
<td>0.5</td>
<td>8</td>
<td>(–)</td>
<td>59.8 (–)</td>
</tr>
<tr>
<td>11</td>
<td>Synovial sarcoma</td>
<td>Buttock</td>
<td>11 × 11</td>
<td>Micro (+)</td>
<td>3 ×6</td>
<td>1</td>
<td>9</td>
<td>(–)</td>
<td>60 (–)</td>
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<td>(2) Recurrent cases:</td>
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<tr>
<td>12</td>
<td>MFH&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Groin LN</td>
<td>3 × 2</td>
<td>(–)</td>
<td>2 ×4 → 1.5 ×1</td>
<td>0.5</td>
<td>3</td>
<td>115&lt;sup&gt;f&lt;/sup&gt;</td>
<td>36 Wound dehiscence after brachytherapy</td>
</tr>
<tr>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pleomorphic sarcoma Low grade</td>
<td>Retroperitoneum</td>
<td>8 × 8</td>
<td>Gross (+)</td>
<td>2 ×6</td>
<td>1</td>
<td>3</td>
<td>(–)</td>
<td>54 (–)</td>
</tr>
<tr>
<td>14</td>
<td>MFH&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Arm</td>
<td>2 × 2</td>
<td>(–)</td>
<td>2.5 ×6</td>
<td>0.7</td>
<td>2</td>
<td>(–)</td>
<td>45 (–)</td>
</tr>
<tr>
<td>15</td>
<td>Myxoid liposarcoma</td>
<td>Groin</td>
<td>9 × 5</td>
<td>(–)</td>
<td>2.5 ×6</td>
<td>0.5</td>
<td>6</td>
<td>(–)</td>
<td>50.4 Wound infection at the site of flap after brachytherapy</td>
</tr>
<tr>
<td>16</td>
<td>Myxoid MFH</td>
<td>Thigh</td>
<td>1 × 1.5</td>
<td>Micro (+)</td>
<td>2 ×6</td>
<td>0.75</td>
<td>4</td>
<td>110&lt;sup&gt;f&lt;/sup&gt;</td>
<td>54 (–)</td>
</tr>
<tr>
<td>17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>MFH High grade</td>
<td>Buttock</td>
<td>7.5</td>
<td>Micro (+)</td>
<td>2.5 ×8</td>
<td>1</td>
<td>4</td>
<td>24 and 65</td>
<td>60 Wet desquamation during EBRT</td>
</tr>
</tbody>
</table>

<sup>a</sup>Thermoluminescence dosimeter. <sup>b</sup>Malignant peripheral nerve sheath tumor. <sup>c</sup>Malignant fibrous histiocytoma. <sup>d</sup>No evidence of disease. <sup>e</sup>Dead with disease. <sup>f</sup>Disease-free survival. <sup>i</sup>Alive with disease. <sup>j</sup>Patients treated with previous postoperative external beam radiation therapy. <sup>k</sup>In these two patients we did not modify the prescription based on skin dose because tumors were located just beneath the skin.
expected side effects. At the time of resection, the radiation oncologist was also present in the operating room. The surgeon demarcated the area of the tumor bed with clips. Other clips of different sizes were placed to define the critical structures such as major vessels or nerves which ran along the tumor. Then the surgeon put six French catheters parallel to the long axis of the tumor bed with 1–1.5 cm spacing in between (Fig. 1). When the neurovascular bundle or bone was very close to the tumor bed, an effort was made to keep the distance at a minimum of 0.5 cm between catheters and the critical structures by covering the area with muscle or gel-foam. Also, an immediate postoperative CT scan was taken to confirm the distance between the catheters and those structures (Fig. 2). Catheters were secured to the muscles with absorbable sutures in 2–3 different places to preserve the parallel positioning between the catheters. All patients had a single plane implant. The surgeon then placed drains and proceeded with wound closure. The external part of the catheters was secured with silk suture in a purse string manner. On postoperative day (POD) 5, simulation was done for computer planning. The length of coverage with brachytherapy ranged from 1.5 to 17 cm depending on the tumor size. The prescription point was varied between 0.5 and 1 cm from the source axis depending on the distance to the critical structure and the step size was 5 mm. On POD 6, patients received first HDR brachytherapy using Microselectron-HDR (Nucletron, USA) with 10 Ci initial activity of Ir-192 (dose rate 8 Gy/min at a 1 cm distance from the source). The total dose from brachytherapy ranged from 12 to 18 Gy (with 2–3 Gy per fraction, twice a day for 3 days). For the patients who had catheters placed close to the skin, TLD measurement was done on the first day of treatment and the prescription point was moved accordingly. In patient No. 8 whose skin dose was over 100%, the prescription point was changed to lower the dose to the skin. However, in patient Nos 12 and 16, the prescription point was kept as in the initial plan since the tumors were located just beneath the skin.

The interstitial catheters were removed in the radiation oncology department immediately after the last treatment. Three weeks later, the patients resumed EBRT. In one patient, EBRT was delayed owing to a wound problem. The radiation field of EBRT covered the primary tumor volume defined with either MRI or CT scan with a 5 cm margin all around. The total dose was 36–60 Gy with a daily fraction size of 1.8–2 Gy.

Each patient was followed for 13–60 months after the treatment (median 31 months) and underwent a physical check-up every 3 months, chest X-ray every 6 months and yearly MRI or CT scans of the primary sites.

**RESULTS**

All patients completed the planned treatment with good compliance. Even children were able to handle HDR treatment well because they spent only ~5 min in the room by themselves.
At the end of the follow-up, there was no local recurrence in the radiation field (Table 1). However, three patients experienced disease progression. Patient No. 12 with recurrent sarcoma had a newly developed lesion (<1 cm) in the opposite leg 22 months later and underwent wide margin excision with skin graft. She was followed without evidence of disease until the last follow-up date. Patient No. 11 developed multiple lung metastasis 4 months after completion of radiotherapy and subsequent bone and paraaortic lymph node metastases. One (No. 13) of two patients who received reirradiation for recurrent STS developed abdominal sarcomatosis 41 months later.

Wound dehiscence after implantation occurred in one (No. 12) out of 17 patients. The tension from approximating scars was the cause of the wound problem and the patient underwent stapling of the scar with good healing. Another patient (No.15) had wound infection at the site of the flap which healed well without late sequela. Most patients experienced grade 1 or 2 skin reaction, mild erythematous skin changes, from EBRT doses of <60 Gy. However, one patient (No. 8) with liposarcoma of the buttock experienced wet desquamation at the end of external beam radiation and a delayed wound problem which ultimately led to an operation with musculo-cutaneous flap. Another patient (No. 17) who received reirradiation to the same site developed moist desquamation and was managed conservatively.

In long-term follow-up, none of the patients complained about symptoms of neuropathy. Also, there was no-one with edema or necrosis.

**DISCUSSION**

For function preservation in the management of STS, a wide margin resection is the common surgical procedure. Local recurrence rates after conservative surgery alone have been unacceptably high (30–75%). However, surgical resection with combined radiation therapy decreased the local recurrence rate, to <15% (11–15). Many types of radiation treatments such as interstitial brachytherapy (HDR, LDR), EBRT, intraoperative radiotherapy with HDR or a combination of these approaches are being utilized.

In 1985, Hilaris et al. reported that adjuvant brachytherapy using iridium-192 could be effective in eradicating residual sarcoma (16). There was no local recurrence after a median dose of 40 Gy in 4–5 days (0/17). Pisters et al. at the same institution reported long-term results on 164 patients who were randomly assigned either to no further treatment or to adjuvant brachytherapy (42–45 Gy over 4–6 days) after complete surgical resection (1). In the brachytherapy group, there was a definite reduction of local recurrences (13/78 vs 25/86, p = 0.04), with particular benefit limited to high-grade tumors. Also, other reports indicated that reirradiation with brachytherapy could achieve good local control (52 and 68% at 5 years) in patients with recurrent sarcoma (17,18).

On the other hand, others have recommended the standard use of combined brachytherapy and EBRT to maximize the volume of irradiated tissue while at the same time minimizing the wound problems (15,19). Habrand reported results on 50 patients of STS (48 with brachytherapy alone) with a marginal or distant local regional failure rate of 26% (20). These data indicated the necessity for either larger implants or supplementation with EBRT. In contrast, Schray et al. noted that only two local failures out of 65 patients occurred outside the irradiated volume after brachytherapy as a boost and EBRT (15). Especially a brachytherapy boost combined with EBRT may provide better local control in situations where close or positive margins are anticipated. Alekheyar et al. found a trend in favor of brachytherapy boost plus EBRT (90%) rather than brachytherapy alone (59%) as the optimal adjuvant treatment in patients with a positive resection margin (7). In our study, there was no local failure within the irradiation volume from brachytherapy and EBRT, even in nine patients with positive or close surgical margin.

Experience with HDR brachytherapy for STS is limited and more investigation is required in this field. Crownover and Marks reported HDR experience with 10 patients having at least a 1 year follow-up (21). There was no local recurrence and no excessive acute or late sequelae of treatment. They suggested that HDR brachytherapy is an attractive alternative to the LDR technique. Nag and co-workers published reports of HDR brachytherapy in childhood sarcoma and proposed that the combination of conservative surgery, chemotherapy and HDR offers the potential for disease control in young children while preserving bone growth and organ function (9,10).

The optimal dose for HDR has not yet been established. HDR implants are scheduled to replicate the LDR doses that are established as effective. The HDR Brachytherapy Working Group proposed a brachytherapy trial with six treatments of 3 Gy/fraction at 0.5 cm from the plane of implant to be delivered twice daily (total 18 Gy) for microscopic residual disease and with seven treatments (total 21 Gy) for gross residual disease (22). This would be followed by postoperative EBRT. The Cleveland Clinic Foundation recommended the delivery of 36 Gy in 10 fractions for definitive HDR implant to an isodose surface ~0.8 cm from implant plane, twice daily over 5 days and HDR boost treatment of 16.25 Gy in five fractions over 3 days (21). We used HDR brachytherapy as a boost treatment using the prescription point at 0.5–1 cm from the catheters and a total prescription dose of 12–18 Gy (2–3 Gy/fraction).

Early reports by Brennan and co-workers described a high incidence (48%) of major and moderate wound complications with the brachytherapy group compared with 6% in the non-brachytherapy group (3,4). However, later wound problems could be diminished by delaying the loading time of the actual isotope until 5–8 days after operation. The same group reported 14% severe wound complications, which was not different from the non-brachytherapy group (5). Our group started the brachytherapy on POD 6. To reduce the wound complication even further, we tried to avoid the overdose to wounded skin by placing additional tissues between the catheters and the overlying skin. We also measured the skin dose with TLD on the first day of treatment and modified the dose to the skin.
according to TLD measurement by changing the prescription point.

One of the long-term side effects with high doses of EBRT to large volumes is fibrosis and possibly leg edema. Since we reduced the dose of EBRT by using the HDR brachytherapy as a boost, there was very little chronic complication of subcutaneous fibrosis.

Other severe complications have occurred such as neuropathy, especially in the treatment of recurrent tumors. Zelefsky et al. reviewed the experience on patients who had STS involving neurovascular structures and found that neuritis developed after receiving cumulative doses >90 Gy (4/4 vs 0/37 with <90 Gy) (6). However, there was no neuropathy in this study owing to careful placement of catheters and coverage of the neurovascular bundle with muscle or gel-soam as so not to contact these structures with the catheters. Also, a CT scan after the operation was useful in evaluating the relationship between catheters and important anatomical structures.

HDR brachytherapy has some advantages in comparison with LDR. HDR would be easy to utilize as long as the department was equipped with an HDR machine without a special arrangement on the floor. Also, there is no concern about radiation exposure to caregivers. Especially, HDR treatment is convenient with younger children because of the greatly reduced treatment time of only a few minutes and minimal duration of immobilization.

In conclusion, our results suggest that immediate postoperative HDR brachytherapy with EBRT is an effective treatment for the management of STS without local failure inside the radiation field, even in nine patients who had a high risk of local recurrence due to inadequate margins. In particular, there was no neuropathy owing to careful placement of the catheters along the neurovascular bundle. Careful management of the brachytherapy procedure and good cooperation between the surgeon and radiation oncologist should make a good outcome possible with very few side effects. However, this study included only a small number of patients in the analysis, and a longer follow-up is required to observe late complications.

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References