Interstitial Brachytherapy in Soft Tissue Sarcomas: The Rambam Experience

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Abstract

Background: There are radiobiologic and technical advantages to the use of interstitial brachytherapy alone or as an adjunct to external beam radiotherapy in the postoperative treatment of soft tissue sarcomas.

Objectives: To review the experience of the Rambam Medical Center in implementing interstitial brachytherapy in the treatment of 32 patients with soft tissue sarcomas.

Methods: Thirty-two patients with variously located soft tissue sarcomas were managed with a combination of surgery and brachytherapy of the tumor bed, with or without EBRT. In 27 of 32 patients, brachytherapy catheters were placed intraoperatively, while in 5 patients the implant was performed as a separate postoperative procedure. Twenty-seven patients received low dose-rate brachytherapy with Iridium-192 seeds. Five patients received fractionated high dose-rate brachytherapy using the microSelectron machine.

Results: With a median follow-up of 36 months, the overall local control rate was 87.5%. Four of 32 patients (13%) failed locally at the implant site, and 6 (19%) developed lung metastasis. Two of the five patients with lung metastasis had a local recurrence as well. At the time of analysis, eight patients had died of sarcoma (disease-specific mortality rate was 25%), while three had died of intercurrent causes. The 5 year actuarial disease-free survival rate was 56%, and the 5 year actuarial overall survival 70%. Five patients (16%) developed severe wound complications following surgery/brachytherapy, and six patients (19%) developed late local toxicity (fibrosis and telangiectasia).

Conclusions: Wide local excision followed by interstitial brachytherapy has resulted in an 87.5% local control rate with a 16% local complication rate.

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Over the last three decades several strategies have been used to avoid limb amputation while preserving local control rates in soft tissue sarcomas of the extremities. These include wide *en bloc* resection of soft parts, also known as compartmental resection [1,2], pre- or postoperative external beam radiation therapy [3–6], regional intraarterial infusion [7] or perfusion chemotherapy [8], and brachytherapy [9–12]. Each of these treatment methods has its advantages and limitations. The role of local brachytherapy as an adjunct to radical surgery has been explored by several groups of investigators, including the pioneering efforts of the group at Memorial Sloan-Kettering Cancer Center [13–15]. In this paper we report our experience with 32 patients with soft tissue sarcomas in various anatomic locations.

EBRT = external beam radiotherapy

Patients and Methods

Between September 1993 and July 2001, 32 patients with soft tissue sarcomas were managed with definitive surgery and low or high dose-rate interstitial brachytherapy as part of their treatment strategy. Patient characteristics are presented in Table 1. All patients with a soft tissue tumor who were found eligible for general anesthesia and major surgery and who agreed to undergo interstitial brachytherapy under radiation precautionary measures were included. All patients received an explanation of the procedures, and informed consent for surgery and radiotherapy was obtained according to current Israeli requirements. There were 19 males and 13 females; the mean age was 53 years (range 12–90

Table 1. Patient characteristics (n = 32)

Mean age (yrs)	53
Range	12–90
Male/female ratio	19/13
Adults	30
Pediatric patients (<15 years old)	2
Site	
Limbs	19
Superficial trunk	10
Head and neck	1
Abdominal cavity	2
Histopathologic grade	
Low grade or well-differentiated (G-1)	2
Moderately differentiated (G-2)	2
High grade or poorly differentiated (G-3)	28
Stage*	
Stage I	3
Stage II	8
Stage III	21
Histopathologic type	
Malignant fibrous hystiocytoma	12
Leiomyosarcoma	6
Liposarcoma	4
Fibrosarcoma	3
Synovial sarcoma	2
Malignant hemangiopericytoma	1
Malignant schwannoma	1
Primitive neuroectodermal tumor	1
Chondroid syringoma	1
Aggressive fibromatosis	1

* AJCC Cancer Staging Manual, 5th edn. [16]

years). The tumor was located in the limbs in 19 patients, in the trunk (including one patient with a leiomyosarcoma of the pancreas) in 12, and in the neck region in one. Two patients were in the pediatric age group. The patient distribution according to stage [16] is presented in Table 1. In 27 patients the placement of brachytherapy catheters was done intraoperatively, immediately following a wide local excision of the tumor or of the tumor bed after a marginal resection. These 27 patients were initially seen in consultation before surgery/brachytherapy at a multidisciplinary sarcoma clinic that included surgeons (N.M.) and oncologists (E.R., A.K.). In the other five cases, brachytherapy was done post-operatively in patients previously resected with inadequate or questionable margins. These five patients were referred to our clinic following a surgical procedure at another hospital. For this report we have updated the follow-up data on 20 previously reported patients [12] and include an additional 12 patients treated between March 1998 and April 2001. Five of these 12 patients were treated with fractionated HDR brachytherapy.

Intraoperative implantation procedure

Elective wide local excision and intraoperative brachytherapy were recommended in all 27 patients following a biopsy or a marginal excision. Postoperative brachytherapy was done in the five remaining patients operated elsewhere and in whom it was felt that additional surgery could not be performed. In the initial nine patients in this series and following reports by Shiu et al. [14], Harrison et al. [15], and Gerbaulet et al. [17], we attempted to give the entire radiotherapy dose with an implant alone. We observed three cases of severe wound complications following the implant (see Results), and thus we changed our treatment policy, giving only a third of the total radiotherapy dose with the implant and the additional two-thirds by EBRT.

Under general anesthesia a wide local excision was performed, dissecting through the healthy tissue surrounding the tumor except in areas where it came into close proximity with bone or the limb neurovascular bundle. In those areas the tumor was peeled from those structures and brachytherapy catheters were placed above those high risk regions with the interposition of a Gelfoam slab. Following tumor resection, gloves and instruments were changed. After the surgeon completed the tumor resection, the tumor bed was marked with metallic clips for radiologic identification. Under direct visualization a decision was made on the area to be implanted, attempting to cover the tumor bed with an additional 2 cm beyond the actual tumor confines. A series of parallel brachytherapy catheters were percutaneously inserted into the target area, placed between 1.0 and 1.5 cm apart, and secured in position using catgut sutures as required. The entrance and exit points of the catheters were kept at not less than 2 cm from the surgical wound [Figure 1]. The wound was closed by approximation of soft tissue and skin over the catheters, care being taken to leave a drainage tube and thick viable flaps. Plastic and metallic brachytherapy buttons were anchored to the skin with loose stitches at the entrance and exit sites of the catheters.

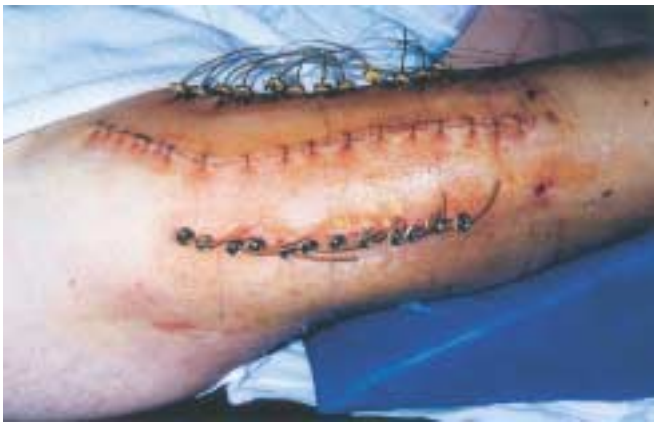

Figure 1. Single-plane LDR implant for a sarcoma of the right leg. Note entrance and exit sites of catheters far from the surgical wound.

Five to 7 days after the surgical procedure, a pair of orthogonal radiographs of the implant with dummy metal sources was obtained for source localization and computerized treatment planning. The implants were then loaded with Iridium-192 radioactive seeds (BEST Industries Inc., Springfield, VA, USA) with an initial activity in the range of 1.25–1.8 mCi per seed. Implants were loaded no earlier than the fifth postoperative day. The median tumor bed implant dose with LDR was 33 Gy (range 18–49 Gy) delivered over 2–5 days. The median dose in the five patients treated with HDR was 16 Gy. The dose was prescribed to an isodose located approximately 0.5 cm from the source plane. This prescribed dose represented the minimal dose within the target volume, the dose between or nearer the radioactive sources being significantly higher.

In 21 of 32 patients, the interstitial implant was used to deliver part (approximately one-third) of the irradiation dose. In these patients the median implant dose was 23 Gy for LDR and 16 Gy for HDR. In 9 of 32 patients, the implant was the sole radiotherapy modality. Hence, in this group of patients the median implant dose was 45.5 Gy (range 45–49 Gy). Variations on the prescribed dose depended on the assessment of clinical variables such as anatomic site and proximity to sensitive structures, prior irradiation, geometric quality of the implants, and the potential risk for wound complications. When the implant plane was relatively close to the skin or neurovascular bundle, lower doses were prescribed (45 Gy). The average implant dose rate was 48 cGy/hour.

Twenty-one of 32 patients (66%) also received EBRT to a median dose of 39.2 Gy (range 16.2–45 Gy). No patient received adjuvant chemotherapy. In the two pediatric patients, chemotherapy was given before the surgical/brachytherapy procedure. A 15 year old boy with a low grade fibrosarcoma of the neck received cisplatin concomitant with EBRT before surgery and brachytherapy. A 12 year old girl with a high grade fibrosarcoma of the left thigh received

EBRT = external beam radiation therapy

LDR = low dose rate
HDR = high dose rate

Figure 2. An 81 year old patient with a high grade pleomorphic liposarcoma of the right arm measuring 8x10x15 cm, following a wide local excision with close margins. Catheters were implanted intraoperatively, and the patient is receiving fractionated HDR brachytherapy.

three courses of ifosfamide-etoposide-mesna before surgery, without response. In five patients, the implant was performed as a separate procedure following a surgical resection with inadequate margins. This was done under local anesthesia and using brachytherapy needles as guides for the brachytherapy catheters in the usual manner.

Since 1998 we have used a microSelectron machine to deliver HDR brachytherapy in five patients with soft tissue sarcomas. In three patients this modality was selected in order to cover an extensive area of resection (chest wall, anterior thigh, and the entire arm) [Figure 2]. In another patient with a large leiomyosarcoma of the pancreas, HDR brachytherapy was given as a single-dose boost following complete resection. The fifth patient was a young male with malignant fibrous histiocytoma of the flank. Following a wide local excision, catheters were placed intraoperatively, and he received 36 Gy in nine fractions as sole definitive adjuvant therapy.

Results

After a median follow-up of 36 months, four patients (12.5%) failed locally, and six (19%) developed lung metastasis. The local control rate for all 32 patients was 87.5% (i.e., 28 patients). The actuarial 5 year survival was 69%, and the actuarial 5 year disease-free survival rate 56%.

At the time of this analysis, eight patients had died of uncontrolled or metastatic sarcoma, and three had died of other causes (rectal cancer, sepsis, and congestive heart failure). Six patients (19%) developed lung metastasis 1–2 years following therapy. Two of the five patients with lung metastasis had a local recurrence as well. In the 27 patients who had an intraoperative implant, the local control rate was 92% (i.e., 25 patients), while in the five patients who underwent a postoperative implant the local control rate was 50%. Table 2 presents an overview of our clinical results.

Complications

Most patients developed variable degrees of erythema of the skin overlying the implant site 7–10 days following brachytherapy. This subsequently subsided. Six patients (19%) developed moderate chronic radiation changes at the implant site (EORTC/RTOG grade 3 toxicity). These changes consisted of various degrees of fibrosis and telangiectasia. In some patients these changes coexisted with cosmetic defects due to the surgical resection of a variable amount of soft tissue.

Table 2. Summary of study results

Variable	Rate (%)
Local control at implant site	87.5
Locoregional failure	12.5
Local control in intraoperative implants	92.0
Local control in postoperative implants	50.0
5 year disease-free survival	56.0
5 year overall actuarial survival	69.0
Local wound complications	16.0
Late tissue toxicity	19.0

We observed five cases of severe complications (16%). These included one local infection, two cases of soft tissue necrosis that healed slowly, one case of painful fibrosis, and one chronic fistula. One of these cases, a 12 year old girl with a high grade fibrosarcoma of the right thigh that did not respond to induction chemotherapy, developed progressive skin and subcutaneous necrosis, with subsequent delay in wound healing and contracture of the knee in the months following the implant. This patient received 45 Gy to the 0.5 cm plane with brachytherapy alone. Soft tissue necrosis was controlled with hyperbaric oxygen therapy, and the knee function impairment resolved with prolonged rehabilitation.

Discussion

Interstitial brachytherapy with Iridium-192 as an adjuvant to radical surgery has already been shown to provide good local control rates in soft tissue sarcomas [9–16]. The use of brachytherapy as an adjuvant to surgery is based on its theoretical and practical advantages over EBRT. The brachytherapy catheters are inserted into the tumor bed *under direct visualization* by the surgeon and the oncologist. Therefore, the high radiation dose is given to a target volume that encompasses the area with the greatest risk of containing residual microscopic disease. Because of the rapid fall-off of the dose with distance, the surrounding tissues are relatively spared. In a prospective randomized trial that included 164 patients, Harrison et al. [15] obtained a local control rate of 82% with complete resection followed by Iridium-192 brachytherapy, compared with 69% with surgery alone ($P = 0.04$). In that trial the improvement in local control was found to be limited to patients with high grade histology, while patients with low grade tumors did not benefit. Adjuvant brachytherapy improved local control, but did not have any significant impact on distant metastasis or tumor-related mortality.

The role of radiation therapy in low grade tumors has not been clearly elucidated. For relatively small lesions that have been completely excised with negative margins, postoperative irradiation is usually not recommended since the majority of these patients are cured by the surgical procedure. In those lesions radiotherapy is usually reserved for patients with positive margins, deep lesions

that are difficult to follow, or questionable margins in a location in which a local recurrence would require amputation. While excision alone has been the most frequent treatment for low grade soft tissue tumors (aggressive fibromatosis, desmoid, dermatofibrosarcoma protuberans), the local recurrence rate in surgical series is as high as 50% [18]. In the present series, brachytherapy was used in four patients with low grade lesions: desmoid tumor, chondroid syringoma, and two cases of low grade fibrosarcoma. In these four patients local control was obtained.

The Memorial Sloan-Kettering Cancer Center experience in the early years of their trial [15] showed more wound complications (11 of 23 patients) when the implants were loaded within the first 5 postoperative days than when the loading was done after the fifth postoperative day (3 of 21 patients). Following those results, we loaded our implants no earlier than the fifth postoperative day. This timing allowed the proliferative phase of wound healing to proceed without being impaired by radiation-induced reduction in fibroblast populations. We observed five wound complications, two of them in patients with probable predisposing factors: an 84 year old woman with diabetes and congestive heart failure and a 12 year old girl pretreated with chemotherapy.

In the largest published series of LDR brachytherapy in children, Gerbaulet and co-workers [17] treated 45 children with 60–75 Gy. After a mean follow-up of 5 years, 78% of the patients were alive and disease-free. A severe complication rate of 18% was observed in 6 of 33 evaluable patients. These six children received doses of between 58 and 75 Gy to the prescription isodose (Paris system), and in those cases the complications probably could be related to the high doses delivered with the implants.

It is still unclear whether brachytherapy should be used alone or in combination with external beam techniques; and, if brachytherapy can be used alone, what would the minimal effective dose be to maintain current local control rates while minimizing wound complication and late toxicity. The American Brachytherapy Society recommends the use of brachytherapy as adjuvant monotherapy for patients with completely resected intermediate or high grade sarcomas of the extremities or superficial trunk with negative margins [19]. Brachytherapy should not be used as the sole treatment modality in the following circumstances: a) if the clinical target volume cannot be adequately covered by an implant, b) if normal tissue tolerance precludes safe delivery of therapeutically meaningful doses with an implant alone, c) if the margins are positive, or d) if there is skin ulceration that raises concern of extensive cutaneous spread via lymphatics.

In addition, there is an ongoing debate about the impact of local control on the development of distant metastasis and disease-specific survival. It seems apparent in most series that a number of patients develop lung metastasis while being controlled at the primary site, probably as an expression of systemic dissemination of tumor cells present, but not diagnosed, at the time of primary therapy. In the present series, 4 of 32 patients developed lung metastasis while being controlled at the primary site, while 2 of 32 developed lung metastasis and a local recurrence simultaneously.

The importance of obtaining negative margins in the resection of soft tissue tumors is well established. It is noteworthy that four of five patients with inadequate margins failed locally, while we observed no local recurrences in the 27 patients who had pathologically adequate margins (>5 mm).

The advantages and disadvantages of HDR brachytherapy will not be discussed here. Experience is accumulating on the use of this modality for soft tissue sarcomas, with promising results [20–22]. The use of HDR brachytherapy as a single modality is particularly attractive in young children with soft tissue sarcomas [22], in whom the use of LDR techniques implies a hospital admission of several days in relative isolation due to radiation precautionary measures. The combination of conservative surgery, chemotherapy, and exclusive HDR brachytherapy to the post-chemotherapy tumor volume with a small margin, avoiding EBRT, could provide local disease control in carefully selected young children, while preserving bone growth and organ function.

We believe that successful results with brachytherapy strongly depend on attention to technical details, such as wide resection with negative margins, marking of the tumor bed with metal clips, adequate coverage of the tumor bed and margins, loading of the implant not earlier than the fifth postoperative day, careful dosimetry, and dose prescription tailored to the clinical situation.

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