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CLINICAL INVESTIGATION **Sarcoma**

SPOT SCANNING PROTON THERAPY IN THE CURATIVE TREATMENT OF ADULT PATIENTS WITH SARCOMA: THE PAUL SCHERRER INSTITUTE EXPERIENCE

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Purpose: To assess the safety and efficacy of spot scanning proton beam therapy (PT) in the curative treatment of soft-tissue sarcoma (STS) in adults patients.

Patients and Methods: We identified 13 STS patients treated with PT between July 1998 and May 2005 in our institutional database. Tumor histology varied with the most common histologic subtypes including liposarcoma and peripheral nerve sheet tumor. All tumors were located in vicinity of critical structures, such as the spinal cord, optic apparatus, bowel, kidney, or bowel. Of the patients, 6 and 5 patients received PT either as adjuvant therapy for non-R0 resection or for recurrence, respectively. Two patients received radical PT for unresectable disease. The median prescribed dose was 69.4 CGE (CGE = proton Gy $\times$ 1.1)–Gy (range, 50.4–76.0) at 1.8 to 2 CGE-Gy (median, 1.9) per fraction. Pre-PT anthracycline-based chemotherapy was delivered to 3 patients only. No patient has been lost to follow-up (median 48.1 months, range, 19.1–100.7 months).

Results: Of the 13 patients, all but 2 patients were alive. Local recurrence developed in 3 (23%) patients. The administered dose to these patients was $\leq$60 Gy-CGE. Distant control was achieved in all but 2 patients (lung metastasis), 1 of whom presented with a concomitant local recurrence. The 4-year local control and metastasis-free survival rates were 74.1% and 84.6%, respectively. Late grade $\geq$2 toxicity was observed in only 2 patients.

Conclusions: Spot scanning PT is an effective and safe treatment for patient with STS in critical locations. The observed toxicity rate was acceptable. © 2007 Elsevier Inc.

Proton beam therapy, Sarcoma, Spot-scanning, Local tumor control.

INTRODUCTION

Soft-tissue sarcoma (STS) constitute a relatively rare group of malignancies representing less than 1% of all cancers in the United States in 2004 (1, 2). These malignancies arise from the connective tissues of the body and occur within any organ or anatomic location. As such, the treatment of STS can be challenging, as it can lie in close vicinity of critical structures or invade these structures extensively. Surgical resection is thus often suboptimal and the delivery of curative radiation dose is likewise problematic in some nonextremity STS. Contemporary management, tailored as a function of tumor-type, stage and histologic grade of the disease, is a combination of nonradical surgery, chemotherapy, and radiation therapy (RT). The rationale of this multidisciplinary approach is to avoid the functional and cosmetic deficits of radical surgery or RT. Dose escalation may improve local control for patients with recurrent disease, close surgical margins or unfavorable tumor sites, such as the deep trunk or head and neck (H&N) location (3–7). Most radiosensitive organs at risk (OARs) can however be found in these latter tumor sites. Consequently, a delivery of highly conformal RT is warranted in these unfavorable cases. Intensity-modulated RT (8) or proton beam therapy (PT) allows one to achieve substantial improvements in the dose distributions for these tumors, when compared with conventional RT. As a result, it has been the PSI policy to deliver high-dose PT to sarcoma patients with recurring tumors or unfavorable primary disease, using the spot-scanning technique (9).

The goals of the present study were to analyze the outcome of STS patients treated with active scanning PT. This is the first published report of clinical results for STS using the PSI spot scanning PT delivery technique.

PATIENTS AND METHODS

Patient population

Between July 1998 and May 2005, 13 patients with nonmetastatic soft-tissue sarcomas (STS) were treated with curative intent at the Paul Scherrer Institute (PSI), Switzerland. The patient characteristics

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are detailed in Table 1. There were 11 STS of the H&N region, proximal upper extremity, superficial pelvis or trunk and two nonvisceral retroperitoneal sarcomas (RPS). Patients were treated with combinations of surgical resection, or biopsy if the tumor was unresectable, and PT, with or without photon RT. After multidisciplinary decision, all patients who underwent biopsy only were considered not amenable to surgery. Eleven patients received PT either as adjuvant therapy for non-R0 resection (gross total removal with positive margins, 4 patients; subtotal removal, 2 patients) or for recurrence (5 patients). Primary tumor according to the American Joint Committee on Cancer (AJCC) stages (10) were as follows: Stage I, 4 patients; Stage II, 2 patients; Stage III, 2 patients. The tumor depth was not recorded consistently and could not be reconstructed reliably. Two patients received radical PT for unresectable disease. All tumors were located in the vicinity of critical structures, such as the spinal cord, brain, or bowel. Two patients presented with a hereditary disorder (von Recklinghausen neurofibromatosis type 1 [NF1] and Gardner's syndrome). Tumor histology were: liposarcoma (n = 3), peripheral nerve sheet tumor (PNST, n = 3), leiomyosarcoma (n = 2), desmoid tumors (n = 2), angiosarcoma (n = 1), spindle cell sarcoma (n = 1), and malignant hemoangioperiocytoma (n = 1). According to the M. D. Anderson Cancer Center criteria's for local failure (MDACC) (11), all patients presented at least one factor predictive of above-average local recurrence risk. These factors were: resection margins, STS localization (H&N, deep trunk), locally recurrent tumor, age >64 years, tumor size (>10 cm), high-grade STS and tumor subtype (MFH, neurogenic and epitheloid sarcoma) (11). Median MDACC local failure risk factor was 3 (range, 2–4). Likewise, a majority of patients (n = 11/13) presented with at least one MDACC risk factor for distant failure (range, 1–3). Two patients received RT before PT. One patient was treated postoperatively with 50.3 Gy for a recurring neurofibroma 43.8 months before PT. Another patient presented with a radiation-induced PNST of the posterior portion of the left maxillary sinus. He underwent accelerated RT 11.9 years before PT for a naso-pharyngeal carcinoma at the age of 17 years. Tumor was initially staged cT4 cNo cMo.

Table 1. Patient characteristics

Characteristic	No. of patients (%)
Age (y)	
Median	41.1
Range	21.8–62.3
Gender	
Female/male	6/7
Presentation	
Primary	9 (69)
Locally recurrent	4 (31)
Tumor location	
Paravertebral, thoracic spine	5 (38)
Paravertebral, cervical spine	1 (8)
Retroperitoneal	2 (15)
Pelvis	1 (8)
Shoulder	2 (15)
Head and neck	2 (15)
Tumor size (cm)	
Median	5.0
Range	1.5–19.0
<5	6 (46)
≥5	7 (54)
Tumor grade	
Low	6 (46)
Intermediate	4 (31)
High	3 (23)
Number of surgical resections	
1	6 (46)
2	5 (39)
≥3	2 (15)
Type of surgery	
Gross total removal	7 (54)
Subtotal removal	4 (31)
Biopsy	2 (15)
Surgical resection margins	
Positive	13 (100)
Negative	0 (0)

The median preoperative tumor volume was 80.5 cm^3 (range, 3.4–1572.5 cm^3). No preoperative radiation therapy or chemotherapy was delivered. Only 3 (23%) patients received postoperative anthracycline-based chemotherapy. Before radiation therapy, another patient received systemic treatment, consisting of sulindac and tamoxifen. The median duration of the follow-up for the surviving patients was 48.1 months (range, 19.1–100.7 months). All patients had a follow-up of at least 1 year and all but 1 had a follow-up of at least 2 years. No patient was lost to follow-up.

Treatment planning and delivery

Three-dimensional CT-based treatment planning was employed for every patient. Treatment was delivered with protons only (n = 6) or with protons and photons (n = 7). Because of scheduling constraints at the PSI, the dose given with protons as a fraction of total dose was variable, within a range of 17% to 73% (median, 40%). The PT was delivered with spot-scanning technology. This operational technique enables the proton pencil beams to be scanned within the tumor volume in three-dimensions using a magnetic sweeping of the beam, a mechanical automated table movement and sequential polycarbonate sheet absorbers (*i.e.*, range shifters plates). This technique has been described in detail elsewhere (9, 12). Typical treatment plans are displayed in Fig. 1A to 1C. For the PT planning, the gross tumor volume (GTV) was defined as the preoperative tumor volume identified on the diagnostic CT-MRI for all patients and the preoperative tumor volume, including the residual sarcoma identified on the planning-CT, for 4 patients who underwent sub-total resection (Table 1). The clinical target volume (CTV) included the GTV, the operative bed, plus regions of suspected microscopic spread. The planning target volume (PTV) encompassed the CTV plus a margin of 5 to 25 mm (median, 7.5 mm). The PTV was defined taking into account the presence of natural anatomic barriers in adding the margins and efforts were made to spare portions of organs at risk (OARs). The GTV, CTV, and PTV ranged from 8.5 to 85.3 cm^3 (median, 40.3 cm^3), 23.2 to 631.1 cm^3 (median, 161.3 cm^3), and 46.9 to 1365.7 cm^3 (median, 247.6 cm^3), respectively.

Dose constraints to the surrounding OARs were set based on published data and clinical experience: maximum dose of 54 and 63 CGE-Gy to the center and surface of the brainstem (13) and spinal cord (14). For thoracic, abdominal and pelvic tumor location, no dose-constraints were applied to the lung, heart, esophagus, bowel, and kidney, as the delivered dose with protons were always under the tolerance dose-threshold defined by Emami *et al.* (15). Optic chiasm and nerve dose constraints were 54 and 56 CGE-Gy, respectively. If clinically indicated, the treating physician had the option to relax the OAR's dose constraints. All plans were normalized to the mean dose of the PTV. A relative biologic effectiveness factor for protons of 1.1 (relative to ^{60}Co) was used, and proton doses were expressed in terms of Cobalt Gray Equivalent (CGE = proton Gy × 1.1) (16).

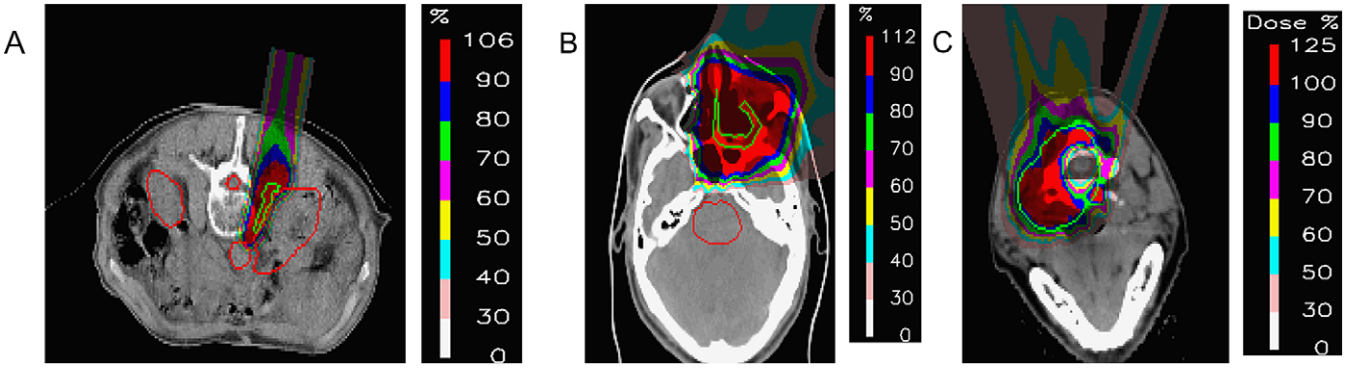

Fig. 1. Dose distribution of a treatment plan for (A) retroperitoneal, (B) head and neck, and (C) paravertebral sarcoma. The isodose color-wash contours are represented by the different colors (corresponding values are displayed on the upper right border of the figure). Note the optimal sparing of the kidney (A), spinal cord (A, C), and brainstem (B). The gross tumor volume (GTV) and organs at risk (OARs; spinal cord, brainstem, kidneys, aorta) contours are outlined in green and red, respectively.

Patients received a median total dose of 69.4 CGE-Gy (range, 50.4–76.0 CGE-Gy). The general institutional policy was to deliver four weekly fractions of 1.8 to 2.0 CGE (median, 1.9 CGE) with PT. Typically, 1 to 6 (median, 2) coplanar (n = 11) or non-coplanar (n = 2) beams were used. The number of fluence modulated Bragg peaks (*i.e.*, spots) delivered per field ranged from 836 to 15,486. With the current delivery rate of approximately 3000 Bragg peaks per minute, this translated into delivery times per field of between a few seconds to 5 min. To optimize target coverage, while respecting OAR-dose constraints, 2 patients were treated with intensity modulated PT. Seven patients were also irradiated with high-energy photons, to a dose ranging from 18 to 50.4 Gy (median, 41.4 Gy) (weekly fraction 5 × 1.8–2.0 Gy).

Follow-up evaluation

Follow-up was obtained by office visit in the author's clinic (DCW), correspondence with the referring physician, or by direct telephone contact with the patient. Acute toxicities were defined as those adverse events that occur from the day of the treatment through day 90. All side effects seen after 90 days from the end of PT were considered late complications. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading system (http://ctep.cancer.gov).

Statistical analysis

Overall, progression-free (PFS) and complication-free survival times were determined from the date of the first day of PT. The major endpoints of this study were local recurrence (defined as any recurrence at or adjacent to the initial primary site), regional recurrence (any recurrence in the regional lymph nodes), metastatic recurrence (any hematogenous recurrence), and freedom from progression (*i.e.*, PFS for which the first recurrence at any site is an event). Survival rates were calculated using the actuarial method of Kaplan and Meier (17). Observations were censored on death or end of follow-up for survival and tumor control endpoints. Survival analysis and descriptive statistics were performed with the software program StatView (version 5.0, SAS Institute Inc., Cary, NC, or http://www.statview.com/).

RESULTS

Outcomes

Patient outcomes are summarized in Table 2. At the time of the analysis, 3 patients had developed with a local failure.

Table 2. Outcomes of all 13 soft-tissue sarcoma patients treated with spot-scanning proton therapy

Case institutional no.	Age (y), gender	Tumor grade	Disease status	RT dose (Gy-CGE)	Follow-up time (mo)	Time to LF (mo)	Time to DF (mo)	Outcome
02017	60.6 F	Low	Recurrent	50.4	47.7	5.0	5.0	AWD
99006	35.8 M*	Low	Primary	60.0	37.6	18.1	—	Dead
02015	21.8 F*	Low	Primary	54	50.5	10.1	—	AWD
02032	32.9 M	High	Recurrent	66.6	18.4	—	0.4	Dead
02010	62.3 M	Intermediate	Primary	73.8	52.8	—	—	NED
00022	55.4 M	High	Primary	70.2	75.1	—	—	NED
03038	27.0 M	Intermediate	Primary	65.5	37.2	—	—	NED
01005	55.5 F	Intermediate	Primary	72.0	48.1	—	—	NED
00014	53.0 M	Low	Recurrent	70.0	70.7	—	—	NED
98001	55.6 M	Intermediate	Primary	69.4	100.7	—	—	NED
05035	21.8 F	Low	Primary	60.0	19.1	—	—	NED
03035	30.8 F	High	Primary	76.0	42.3	—	—	NED
04024	41.1 F	Low	Recurrent	64.0	25.6	—	—	NED

Abbreviations: AWD = alive with disease; CGE = Cobalt Gray equivalent; DF = distant failure; F = female; LF = local failure; NED = no evidence of disease; M = male; RT = radiation therapy.

* Patient with an inherited genetic disorder.

One hemangiopericytoma patient presented with a local failure with concomitant lung metastasis, 5 months after PT. She underwent successfully two surgeries on the thoracic spine. One surgical procedure was done with a chemo-embolization procedure. She is presently well and asymptomatic 47.7 months after radiation therapy. Another patient with an extensive desmoid tumor developped a tumor progression 10.1 months after PT. She was known for Gardner syndrome, with a FAP germ line mutation. Imatinib targeted therapy and subsequently chemotherapy (metotrexate and vinblastine) was administered. No objective response was observed with these systemic therapies. She subsequently underwent two further non-R0 tumor removals and one radiofrequency thermo-ablative procedure. This patient is home-bound and symptomatic 50.5 months after radiation therapy. Finally, a PNST patient presented with a tumor progression 18.1 months after PT. He was diagnosed 15 years earlier (benign fibroma of the left knee). Chemotherapy was delivered with an objective response (4 cycles of ifosfamide-doxorubicin). He subsequently progressed and received additional chemotherapy (ifosfamide-doxorubicin and topotecan-cyclophosphamide) with no response. He developed 2 years after PT an intestinal gastrointestinal stromal tumor (GIST), diagnosed incidentally after intestinal bleeding. The patient died in a cachectic state with local recurrence and a paraneoplasic syndrome 37.6 months after PT. Thus the estimated 4-year local control rate was 74.1% (Fig. 2). No regional failure was observed.

Two patients presented distant failures (Table 2). One hemangiopericytoma patient presented lung metastases, with a concomitant local failure. Another PNST patient presented with one lung metastasis shortly after PT (0.4 months). He had a medical history significant for a recurring neurofibroma that was excised three times within a 9-ear period. He had no diagnostic criteria for NF1 (18). After the third subtotal resection he underwent postoperative RT (50.3 Gy, 31 fractions of 1.7 Gy). He subsequently recurred and underwent a fore-quarter amputation, 11 months before PT. As a result of a fifth recurrence, this non-NF1 patient was offered PT only. After PT, he underwent ifosfamide-doxorubicin and high-dose chemotherapy ifosfamide after a symptomatic tumor-progression in the lung. A lung metastatectomy was performed 8.7 months after PT. He subsequently underwent gemcitabine chemotherapy and was offered after targeted therapy (gefitinib) for a nonlocal tumor progression (bone and cervical intradural spinal cord metastases). Subsequently, lower extremities paralysis developed and this locally-controlled patient died 18.4 months after PT. Noteworthy, both patients were treated for recurrent disease. Before PT, both patients underwent 4 surgerical procedures and no chemotherapy was delivered for these multiple recurrences. Thus, the estimated 4-year metastasis-free survival and PFS rates were 84.6% and 68.4%, respectively.

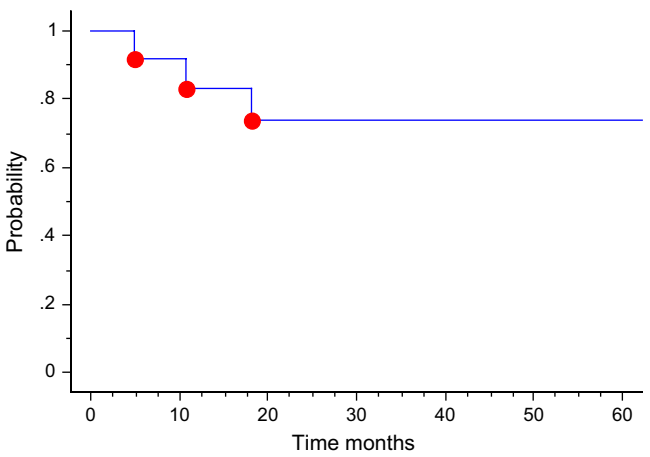

Fig. 2. Actuarial local control in soft-tissue sarcoma patients (n = 13) treated with spot-scanning proton beam therapy.

Two patients died in our series 18.4 and 37.6 months after PT, both of tumor progression (Table 2). One died as a result of distant and local tumor progression. The other died from extensive lung, bone, and spinal cord metastasis, with a primary PNST controlled. Thus, the estimated 4-year overall survival rate was 82.5%.

Adverse events

The most common transient acute side effects were skin erythema (Grade 1–3) and dysphagia (Grade 2). Of note, the patients with retroperitoneal or pelvic tumors did not develop clinically significant intestinal discomfort. No diarrhea was observed. One H&N patient presented with homolateral grade 2 conjunctivitis.

Late adverse events were observed in 2 (15%) patients. One bus driver patient with radiation-induced PNST in the H&N region (left maxillary sinus) presented with a symptomatic left sub-capsular cataract 34.8 months after PT. For this patient, maximum, mean and minimum dose to the left lens were 62.2, 57.7, and 52.2 CGE-Gy, respectively. Of note, this complication was listed on the informed consent signed by the patient before PT. He underwent successfully a phakectomy and is now free of any visual symptoms and professionally driving his bus 38.6 months after PT. Of note, the other H&N angiosarcoma patient received a maximum, mean and minimum dose to the lens of 45.4, 40.8, and 36.6 CGE and did not present with this complication 40.2 months after treatment. The second patient presented a symptomatic Grade 3 brain necrosis 28.6 months after PT. She was treated for a paranasal sinus angiosarcoma with protons only (76 CGE). She subsequently presented with Grade 3 headaches and a MRI showed gadolinium enhancement in the internal aspect of the left temporal lobe. O-(2-[18F]fluoroethyl)-L-tyrosine PET showed an abnormal uptake, compatible with tumor recurrence. Consequently, she underwent an open craniotomy and the histologic diagnosis of brain necrosis was made. No tumor was identified in the pathologic specimen. For this patient, maximum dose to the left temporal lobe was 79 CGE. Again, this complication was listed on the informed consent signed by the patient before PT. Corticosteroids were successfully tampered and she is now asymptomatic and well 40.2 months after PT. The estimated 4-year TFS grade $\geq$2 is thus 77.8% (Fig. 3).

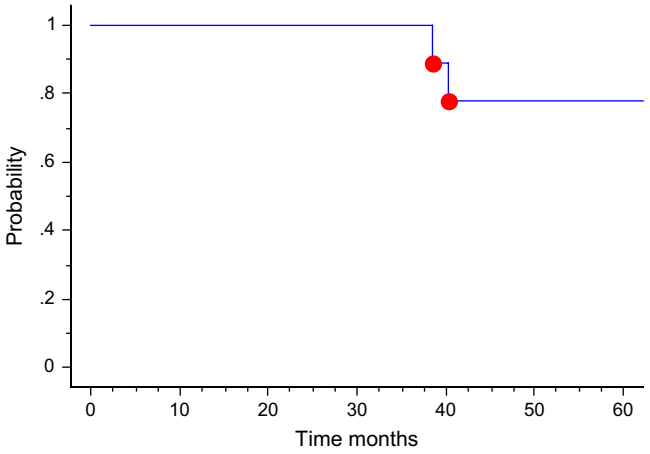

Fig. 3. Actuarial toxicity-free survival for soft-tissue sarcoma patients (n = 13) treated with spot-scanning proton beam therapy.

Three patients presented second malignancies after treatment. These cancers were clearly outside the irradiated areas and were thus considered non–radiation-induced malignancies. One leiomyosarcoma patient 55 years of age presented with a left foot skin melanoma. This skin malignancy occurred 70 months after PT. He underwent successfully curative surgery and has currently no evidence of disease, 75.1 months after PT. The second patient was 36 years of age and was diagnosed with NF1 before PT (Table 2). He presented a GIST, 21.6 months after treatment. Finally, a 63 year-old liposarcoma patient developed 28.3 months after PT a high-grade fusocellular sarcoma of the left thigh. He underwent curative limb sparing non-R0 surgery and postoperative photon RT (64.8 Gy). No chemotherapy was administered. This patient is also disease-free, 52.8 months after PT.

DISCUSSION

The observed cumulative 4-year local control and metastasis-free survival rates of 74% and 85% compare favorably with other large STS (11, 19) and RPS (20, 21) photon RT series. Although a number of dose-comparative studies have been published for sarcoma (8, 22), the tumor types included in this mature series, with a median follow-up of 4 years, have exceptionally been treated with particle therapy with protons or heavier ions. Nowakowski *et al.* reported on 10 STS patients treated helium and neon particle beams (23). The delivered dose ranged from 50 to 76 (median, 66) Gy-Equivalent for this population of patients treated with multiple surgical procedures and incomplete tumor resection. Median follow-up was 28 months. The crude local control was achieved in 6 of 10 (60%) patients. The median time to failure was 5.8 months, although 1 patient was controlled for 60 months. Using these hadrons, toxicity was however observed in a substantial number of patients, including, but not limited to, spinal cord or brachial plexus injury, and subcutaneous fibrosis. These types of complication were not observed in our series consisting of a majority of patients presenting with shoulder or paraspinal tumors (Table 1). Likewise, Weber *et al.* have previously reported on two sinonasal sarcomas treated with photon/proton RT (24). Total delivered dose were 66.2 and 67.8 Gy-CGE, respectively. After a follow-up of 23.5 and 53.3 months, 1 patient had no evidence of disease, and another died of local recurrence only months 12.2 months after RT. No visual or nonvisual complications were observed.

It was generally accepted that sarcomas are radioresistant tumors. This concept was established before the development of modern linear accelerators, at a time when only orthovoltage RT could be delivered to tumors, when these malignancies were generally suboptimally imaged and surgically resected (25). Although tumor cells may show a very broad range of *in vitro* survival curves after radiation, and that spectrum of radiosensitivity tend to somewhat overlap, it is conventionally considered that cells from sarcoma are more radiosensitive than those from squamous cell carcinoma (26). Dose escalation studies have reported improved local control as the radiation dose is raised (4, 27–29), whereas others have found no such relation (7, 30–32). Zagars *et al.* have analyzed this conflicting postoperative dose-tumor control relation in a cohort of 775 STS patients (3). In multivariate analysis, radiation dose ≥64 Gy was independently correlated with improved local control. This correlation between increased effectiveness of higher dose was particularly apparent with H&N tumor location, non-negative margins and recurrent disease. Likewise, Tepper *et al.* reported on a series of 17 RPS patients treated with postoperative RT (33). The observed 5-year local control rate was only 33% of those patients receiving ≤50 Gy, whereas those treated with >50 Gy had a >90% local control rate. Consequentially, it was our clinical practice to propose to patients with these sarcoma-characteristics (RPS or H&N STS, with or without positive margins, or recurrent disease) to undergo PT, as these selected patients probably most benefit from high-dose RT. Of note, all patients presented a risk factor for local failure and all but 2 patients had an unfavorable risk tumoral profile for distant failure. The observed rate of local and distant failure observed in our series for these high-risk patients is exemplified by the remarkable outcome of a patient presenting with a large (18.5 × 10 × 8.5 cm) high-grade leiomyosarcoma (adverse histotype), treated with postoperative chemotherapy and photon/proton RT (70.2 Gy-CGE) who remained with no evidence of disease >75 months after treatment. We do not have the prescience to declare that the control of the disease achieved for these high-risk patients resulted from PT, but it is not unreasonable to think the delivered high dose of radiation might have contributed to the favorable outcome of these patients. This dose escalation strategy in selected patients is being pursued by other groups (34).

No statistical analysis has been performed, as a result of the limited number of events in this small cohort of sarcoma patients. The STS is a highly heterogeneous tumor category with numerous prognostic variables. Univariate analysis even in a large cohort of patients can be misleading, as these variables seriously confound the interpretation of the data.

Multivariate analysis is the only correct statistical method when multiple factors affect an end point. The number of events in our series obviates any possibility of doing such statistical analysis. It is noteworthy that the administered dose and the presentation status in our study influenced outcome. All patients receiving ≤60 Gy-CGE recurred locally, whereas none receiving > 60 Gy-CGE presented a local failure (Table 2). Half of the patients treated for recurrent disease failed distantly, whereas no patients with primary disease develop this pattern of failure (Table 2). Likewise, the 2 patients with a hereditary condition did poorly. Possible explanations for this latter finding include imbalances between the two groups with respect to known and unknown baseline prognostic factors or, most likely, ''statistical'' chance. One Gardner syndrome patient had a very large (>20 cm) tumor that failed several systemic therapy and was controlled for less than 1 year with PT. The NF1 patient progressed 18 months after PT. The evolution of NF1 patients is typified by the malignant transformation of a neurofibroma to a PNST, that causes significant morbidity and mortality, and our patient was no exception to this type of outcome. PNST is the most important cause of mortality in adult patients with NF1 less than 40 years of age (35). The outcome of the other non-radiation induced PNST was however also remarkable. The biologic aggressiveness of this low-grade tumor was striking, the patient progressing rapidly when not receiving systemic treatments. This tumor is considered a high-risk sarcoma subtype for local failures (11) and should be thus aggressively treated. In retrospect, the delivery of 60 CGE to the NF1 patient was too conservative a dose to optimally control his STS. In this series, a higher dose (mean, >66 Gy-CGE) delivered to the other PNST patients managed to avoid any local failure. Conversely, the patient with the radiation-induced PNST had a favorable outcome. Radiation-induced sarcoma may not be tantamount to poor prognosis (36), and selected patients should be treated optimally with curative intent.

There were several limitations of our study. First, the small sample size of 13 patients, with various histologic subtypes, treated over several years limits the general conclusions and findings of this sarcoma series. This is particularly true for the association of hereditary disorders and poor outcome which were based on the two index cases reported. Second, the factors used as prognosticators in our patients derived from non-RPS series (11). The prognosis significance of these factors may be only partially valid for RPS, although the importance of negative margins 37 and histologic grade (21, 37, 38) and tumor type (21) has been demonstrated in large PRS series. This choice was however made as a result of the very limited number (n = 2) of RPS patients in this series. Third, we did not exclude idiosyncratic variants, such as desmoids or angiosarcoma—as recommended by the AJCC (10)—as a result of the limited number of patients, increasing somewhat the heterogeneity of these tumors in this series. Finally, although the median administered dose in this series was high, certain patients received ≤60 CGE-Gy, as a result of hereditary disorders or patient refusal to receive higher radiation doses. It is noteworthy that all these patients treated with less that this dose cut-off locally progressed. As a result of this analysis, our dose prescription-policy has been consequentially increased.

In summary, high-dose spot-scanning PT achieved a high rate of local control for these high-risk STS patients. The observed local control rate in this series did not come at the expense of significant radiation-induced morbidity. Larger number of patients is needed to more fully evaluate the results of PT, using spot scanning technology, administered to high-risk sarcoma patients.

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