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Proton irradiation in sarcoma

# A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma

David M. Guttmann [a,*], Melissa A. Frick [a], Ruben Carmona [a], Curtiland Deville Jr. [b], William P. Levin [a], Abigail T. Berman [a], Chidambaram Chinniah [a], Stephen M. Hahn [c], John P. Plastaras [a], Charles B. Simone 2nd [d]

[a] Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia; [b] Department of Radiation Oncology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore; [c] Division of Radiation Oncology, MD Anderson Cancer Center, Houston; and [d] Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, United States

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ABSTRACT

*Background and purpose:* Proton reirradiation for sarcoma has not been previously described. We hypothesized that this strategy would provide favorable toxicity and survival outcomes.
*Material and methods:* Patients with soft tissue sarcoma in a previously-irradiated field were enrolled on a prospective trial of proton reirradiation. The primary endpoint was provider-reported acute toxicity. Secondary endpoints included late toxicities, local control, and overall survival.
*Results:* 23 patients underwent proton reirradiation. Median time between radiation courses was 40.7 months (range 10–272). No grade 4–5 toxicities were observed. One patient (4%) experienced acute grade 3 dysphagia. Common grade 2 acute toxicities were fatigue (26%), anorexia (17%), and urinary incontinence (13%). There were two grade 3 late wound infections (10%) and one grade 3 late wound complication (5%). Grade 2 late complications included lymphedema (10%), fracture (5%), and fibrosis (5%). At a median follow-up of 36 months, the 3-year cumulative incidence of local failure was 41% (95% CI [20–63%]). Median overall survival and progression-free survival were 44 and 29 months, respectively. In extremity patients, amputation was spared in 7/10 (70%).
*Conclusions:* Proton reirradiation of recurrent/secondary soft tissue sarcomas is well tolerated. While longer follow-up is needed, early survival outcomes in this high-risk population are encouraging.
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Soft tissue sarcomas recurring or developing in previously irradiated tissues represent a significant morbidity burden and treatment challenge for cancer patients. Following multimodality treatment involving radiotherapy and surgery with extremity soft tissue sarcoma, up to 15% of patients will develop a local recurrence [1]. The recurrence rates are even higher in retroperitoneal or skull base sarcomas [2–4]. In addition, radiation-induced sarcomas develop as a complication of treatment in approximately 0.1% of patients treated with radiotherapy for other primary tumors [5]. Secondary sarcomas from a prior radiotherapy course may become a more prevalent condition in the future as we continue to extend survivorship from pediatric and other malignancies [6].

For patients who present with a sarcoma in a previously-irradiated field, management options include radical resection (e.g. amputation) or wide local excision, systemic therapy, and/or reirradiation. When a radical resection is not feasible, such as in cases of patient refusal or medical inoperability, incorporating reirradiation into treatment can present challenges due to the toxicities of delivering a high radiation dose to previously-irradiated tissue. Critical structures that may have received doses close to their maximum safe tolerance during the first course of radiotherapy limit our ability to safely reirradiate at recurrence. Proton radiotherapy may mitigate such toxicity through its characteristic rapid dose fall-off at the distal edge of the beam, sparing distal tissue from radiation dose completely [7,8]. Therefore, we hypothesized that proton therapy would offer a safe and effective means of reirradiation for patients with recurrent or new primary soft tissue sarcoma. Here, we report the results of the first published prospective study of proton reirradiation for soft tissue sarcoma.

## Materials and methods

### *Patient enrollment*

Patients providing informed consent were enrolled on an institutional review board-approved prospective feasibility trial of reirradiation with proton therapy at our institution (NCT01126476).

* Corresponding author at: Department of Radiation Oncology, University of Pennsylvania, Perelman School of Medicine, 3400 Civic Center Boulevard, TRC 2 West, Philadelphia, PA 19104, United States.
*E-mail address:* david.guttmann@uphs.upenn.edu (D.M. Guttmann).

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Inclusion criteria for enrollment included Karnofsky Performance Status >60 and life expectancy of at least 3 months. Any patient with soft tissue sarcoma as classified in the WHO Classification of Tumors of Soft Tissue and Bone [9] was eligible. Tumors were required to overlap the 50% isodose level or higher from the prior course of radiotherapy. Patients were able to undergo additional surgery at the time of recurrence if they were felt to be operable and radiotherapy could be administered in a neoadjuvant or adjuvant fashion. Definitive intent treatment was administered for non-operable patients. Patients were ineligible if less than 3 months had elapsed since their first course of radiotherapy. Patients with metastatic sarcoma prior to reirradiation were excluded from this analysis.

### *Target contouring and radiation treatment planning*

Proton therapy was delivered using passive scattering or active scanning (uniform scanning or pencil beam scanning [PBS]). For passive scattering, Lucite compensators and multi-leaf collimators were used for beam shaping and distal edge conformality. For active scanning, target coverage and conformality was achieved through modulation of the proton pencil beam.

Proton radiation therapy was planned from CT simulation, additionally using MRI or PET/CT fusion when applicable. When indicated, a 4-dimensional CT scan was used to define the extent of target motion. Target volumes for gross tumor volume (GTV), clinical tumor volume (CTV), and internal target volume (ITV) where applicable, were contoured according to ICRU recommendations [10,11]. A CTV margin of 5–10 mm was incorporated to account for microscopic spread, and an ITV margin (when appropriate) was added after observing the extent of target motion on the 4-dimensional CT. For planning, an additional margin of 3.5% of the water equivalent thickness of tissue along the beam path plus an additional 1mm for PBS or 3 mm for double scatter plans was added in the direction of the beam's eye view to account for range uncertainty in conversion of CT number to proton stopping power [12,13]. In addition, to evaluate target coverage, a traditional PTV expansion was created from the CTV, generally using a 5 mm uniform expansion. Target coverage was recommended such that 99% of the CTV/ITV was covered by 98% of the prescription dose and 98% of the PTV was covered by 95% of the prescription dose.

Organs at risk (OARs) were contoured and dose to OARs was calculated by generating a cumulative plan sum dose distribution from the initial and retreatment radiation plans applied to the retreatment scan. Absolute constraints were applied as follows: spinal cord maximum cumulative point dose of 75 Gy (assumes approximately 50% recovery from the initial radiotherapy course); liver total median cumulative dose of 50 Gy; and kidney median cumulative dose of 30 Gy. Other OAR dose constraints, prescription doses, and decisions on treatment intent (neoadjuvant, definitive, or adjuvant) were left to the discretion of the treating physician, taking into account prior radiation dose, organs at risk, recovery time, and treatment sequence. Conventional fractionation (1.5–2.0 Gy per fraction) with daily treatment was encouraged.

### *Patient follow-up and evaluation*

All patients were evaluated prior to treatment, weekly during the course of the treatment, 1 month post-radiation completion, and then for a minimum of 90 days after initiation of radiation treatment. Each follow-up examination included interval history and physical examination, toxicity assessment, and clinically indicated laboratories. After 90 days, patients were then followed generally every 3 months in years 1–2, every 4–6 months in years 3–4, and then annually thereafter.

The primary objective was to assess acute toxicity and feasibility of proton reirradiation. Secondary objectives included estimating rates of late toxicity, local control, and overall survival. Data on acute toxicity, defined as occurring within 90 days from the start of radiation therapy, was scored using CTCAE v4.0. Acute toxicity data were collected weekly on treatment and during follow-up visits within 90 days from the start of treatment. Late toxicity was defined as any time thereafter, and toxicity assessments were obtained at every follow-up visit. All toxicity data were reported as the worst toxicity at a single time point. Local control was assessed on follow-up imaging and defined as stabile appearance of disease on serial scans. Local failure was defined as growth on follow-up imaging. Local failure was considered as in-field if it developed within the CTV of the reirradiation course and regional if it was within neighboring tissues.

### *Statistical analysis*

Descriptive statistics were used to summarize baseline demographic and clinical factors of the population and to report on toxicity outcomes. Overall survival was determined from the date of diagnosis of the recurrence or secondary sarcoma until death from any cause. Progression-free survival was defined as the time from diagnosis of the recurrence or secondary sarcoma to the first evidence of local failure, distant failure, or death from any cause. Local and distant failures were assessed via imaging but confirmed by biopsy when clinically feasible. Local failure and distant failure were defined as first radiographic or pathologic evidence of disease recurrence within the treatment field region or at a distant site. Overall survival and progression-free survival were analyzed using the Kaplan–Meier method. Local failure was estimated using the cumulative incidence function with distant failure and death as competing risks. Analyses were performed with the Stata software package (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX) and R version 3.0.2 (www.R-project.org; cmprsk package). For all studies, level of significance was determined by a two-sided type I error rate of $\alpha < 0.05$.

## Results

### *Patient characteristics and treatment*

From March 2010 until September 2016, 23 patients with locally recurrent or new primary sarcomas in previously irradiated fields were prospectively enrolled. The treatment intent in all cases was to control the only known site of disease.

Patient characteristics and treatment details are provided in Table 1. 20 patients (87%) were ECOG 0–1. The median time between radiation courses was 40.7 months (range 10–272), although the first case of reirradiation where overlapping dose was delivered to the spinal cord was administered after a treatment interval of 17 months. All courses of reirradiation with shorter treatment interval were extremity patients. The median follow-up after reirradiation was 36 months. Six patients had initially presented with non-sarcoma primary tumors and were under treatment for a secondary sarcoma, whereas the remainder had experienced a local recurrence of their previously irradiated primary sarcoma. Surgery was a component of treatment in 22 (96%) patients during their initial diagnosis, and 70% had been initially treated with 3D conformal radiation to a median dose of 5040 cGy, most commonly in 180 cGy daily fractions.

Liposarcoma was the most common histology of recurrent or secondary sarcoma (26%). The majority of patients were Grade 3 (52%) sarcomas, and the median tumor size was 5.0 cm (IQR 4.6). Surgery was performed for treatment of the local recurrence of the original cancer or secondary sarcoma in 15 cases (65%) in con-