

Scientific Article

Preoperative Stereotactic Body Radiation Therapy for Soft-Tissue Sarcoma: Results of Phase 2 Study



Gregory J. Kubicek, MD,^{a,*} Tae Won Kim, MD,^b Christina J. Gutowski, MD,^b Maureen Kaden, BS,^b Gary Eastwick, MD,^a Polina Khrizman, MD,^c Qianyi Xu, PhD,^a and Richard Lackman, MD^b

^aDepartment of Radiation Oncology, Cooper University Hospital, Camden, New Jersey; ^bDepartment of Orthopedic Surgery, Cooper University Hospital, Camden, New Jersey; ^cDepartment of Medical Oncology, Cooper University Hospital, Camden, New Jersey

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Abstract

Purpose: Preoperative radiation followed by surgical resection is a standard treatment for soft-tissue sarcomas (STS). We report on 2 consecutive, phase 2, single-arm studies evaluating 5 fraction stereotactic body radiation therapy (SBRT) treatments followed by surgical resection for STS (clinicaltrials.gov NCT02706171).

Methods and Materials: A total of 16 patients were treated with preoperative SBRT. Tumor size in the greatest dimension was a median 6.7 cm (maximum: 14 cm) and the majority of STS were in the extremities. SBRT consisted of 35 to 40 Gy in 5 fractions every other day.

Results: Median follow-up time was 1719 days (4.7 years). Grade ≥ 3 acute toxicity occurred in 1 patient (grade 3 skin changes). Fifteen patients proceeded with surgical resection. Three patients had a wound complication after surgery, 1 patient had grade ≥ 3 late toxicity (grade 4 requiring surgical intervention). There was 1 local recurrence and 5 distant recurrences.

Conclusions: Long-term follow-up on SBRT for STS found acceptable control and toxicity rates, and warrants further evaluation.

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Introduction

Radiation therapy (RT), consisting of either pre- or postoperative treatment¹⁻³ has been shown to improve local control for soft-tissue sarcomas (STS) in combination with surgical resection. Several studies have found that more advanced radiation techniques, including image

guided radiation⁴⁻⁵ and intensity modulated radiation,⁶⁻⁸ have reduced toxicity while preserving local control rates. Radiation Therapy Oncology Group study 0630 investigated image guided radiation with a reduced target volume and median follow-up of 3.6 years, and reported an 11.4% 2-year local failure rate and 10.5% toxicity rate.⁵ O'Sullivan et al. reported on their experience using image guided intensity modulated radiation, with a 30.5% complication rate and 6.8% local failure rate.⁴

The aforementioned studies point to improvements that can be realized with more precise radiation delivery. Several studies have looked at different radiation schedules, using higher radiation doses per fraction (hypofractionation) to allow for a reduction in treatment time.

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*Corresponding author: Gregory J. Kubicek, MD; E-mail: greg.kubicek@gmail.com

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These studies also had higher failure rates, likely secondary to lower overall radiation doses.⁹⁻¹⁰ The technology available in these studies limited the amount of radiation that could safely be delivered per fraction.

An option to further improve on these results is the use of stereotactic body radiation therapy (SBRT), which uses high-dose radiation with a high degree of precision.¹¹ We hypothesize that the higher dose per fraction of the SBRT technique may be more effective than standard dosing schedules given the radio resistance of STS. We reported on our initial experience with this technique,¹² and initiated prospective phase 2 studies based on these results. Subsequently, several institutions have reported on their experience using 5 fraction preoperative radiation, and also found favorable toxicity results.^{13,14} This is the report of our completed phase 2 studies with long-term follow-up of SBRT for the preoperative treatment of STS.

Methods and materials

Patients

This is the long-term report of 2 prospective phase 2 studies (NCT02706171), which were approved by a local institutional review board. The initial phase 2 study (1302) was open to enrollment only for preoperative patients. Patients eligible for the phase 2 study had extremity STS of any histology, indicated for preoperative RT followed by surgical resection. Inclusion criteria required patients to be age >18 years with any comorbid conditions well enough controlled to allow for surgical resection. Chemotherapy could be given either before or after radiosurgery, but there had to be a 1-week break between chemotherapy and SBRT. Surgical resection was planned for 4 to 8 weeks after SBRT. The follow-up phase 2 study (15073) had additional eligibility criteria in that patients with postoperative and definitive (nonoperative) STS were eligible. The follow-up phase 2 study was discontinued before completion of accrual due to changes in department resources. The endpoint for both studies was local control and toxicity.

Stereotactic body radiation therapy technique

All SBRT for this study was performed using the Cyberknife (Accuray, Sunnyvale, CA). Patients had a both a magnetic resonance imaging (MRI) scan with and without contrast and a computed tomography (CT) scan for radiation planning. The CT scan could be done with or without contrast at the discretion of the treating physician. Immobilization used a vac-lock around the target area. Patients were positioned supine or prone depending

on the site of target. Fiducial markers were required for treatment, and could be external if the target was palpable or internal (gold seeds) if the target was nonpalpable.

Gross tumor volume (GTV) was defined as MRI or CT abnormality, including edema on an MRI scan. For study 1302, the planning treatment volume (PTV) included the GTV plus a margin of 0.5 cm radial and 3 cm along tissue plane, which could be reduced to 0.3 and 2 cm, respectively, if there were nearby critical structures (including bone). Study 15073 had slightly different methods, with GTV defined in the same way, but CTV was defined as a 0.2 cm radial margin and 2.5 cm margin along tissue planes, which could be adjusted to a 0.0 radial margin and 1.2 cm tissue plane margin. The PTV included a uniform expansion of 0.3 cm.

Bolus (0.5 cm) could be used to improve the dose to the target at the discretion of the treating physician. Skin was defined as the outer 0.5 cm body surface. The PTV goal was 95% coverage in all patients. There were no dose restrictions, although attempts were made to reduce the dose to the skin and nearby bone. The radiation dose was 35 to 40 Gy in 5 fractions. Patients with deep tumors distant from the skin could be treated to 40 Gy, but most patients received 35 Gy. Treatments were every other day for all patients. Surgery was to be performed 2 to 8 weeks after completion of SBRT.

The biologic equivalent dose (BED) was found by using the following equation:

$$\text{BED} = D \left(1 + \frac{d}{\alpha/\beta} \right)$$

where D is the total dose, d the dose per fraction, and assuming an α/β of 10 for acute responding tissue. SBRT consisted of 5 fractions every other day. The BED for 35 Gy in 5 fractions (2 Gy equivalent) is 50 Gy, assuming an α/β ratio of 10, and would increase to 78 Gy for an α/β ratio of 2.

Toxicity and follow-up

Late toxicities, including lymphedema, fibrosis, and joint stiffness, were scored using the Common Terminology Criteria for Adverse Events, version 4.0. Follow-up was with repeat imaging of the primary site (preferably with MRI) and a CT scan of the chest every 3 months for the first 2 years.

Results

Background information

Sixteen patients were enrolled in this study. Study 1302 was closed after meeting its enrollment goals of 12

patients. Based on the initial success of 1302, a follow-up study (15073) was started with similar eligibility criteria. Study 15073 closed before completing the accrual goals based on lack of research support at the time. Twelve patients were treated in the initial 1302 study, and 7 patients were treated in 15073. Of these 7 patients, 4 were preoperative and 3 postoperative. In total, 16 patients were treated with preoperative SBRT, which is the focus of this analysis. Of the 16 patients treated with preoperative SBRT, most tumors were located in the leg ($n = 12$), followed by the arm ($n = 3$) and trunk ($n = 1$). The most common sarcoma subtype was myxofibrosarcoma (5 patients), followed by liposarcoma and synovial sarcoma (3 patients each). Thirteen tumors were high grade, and 3 were low grade. The median tumor size was 6.7 cm (range, 2.4–14 cm). Thirteen patients had primary disease, with T1 tumors in 5 patients and T2 tumors in 8 patients. Three were classified as recurrent cases, having had previous surgery and development of local recurrence. Two patients had previous radiation to the treatment site (50.4 Gy, 66 Gy), and 3 patients had chemotherapy before SBRT. After completion of SBRT, 1 patient withdrew consent and transferred care, but this patient was evaluable for acute toxicity. Table 1 shows the patient and tumor characteristics.

SBRT consisted of 5 fractions every other day. Fifteen patients had 7 Gy per fraction to 35 Gy, and 1 patient had 40 Gy (8 Gy per fraction). Five patients had a bolus (0.5 cm) used to generate adequate surface dose. Treatment was prescribed to an isodose line with a median of 82%.

Acute toxicity

Acute toxicity consisted of skin changes in 3 patients, and was grade 3 (moist desquamation) in 1 patient (who underwent RT to the ankle using bolus for superficial tumor) and grade 2 skin changes in 2 patients. Two of 3 patients with skin toxicity (including the 1 patient with grade 3 skin toxicity) had a bolus placed to ensure adequate surface dose. In all patients, the skin was healed enough for the planned surgical resection without requiring any delay in surgery (skin changes typically occurred 1–2 weeks after SBRT, and were healed 3–4 weeks after SBRT).

Surgical data

Fifteen patients with evaluable data underwent surgical resection. The median time to surgery was 41 days with a range of 29 to 83 days (delay in surgery for 1 patient was secondary to patient compliance). Resection with negative (R0) margins was achieved in 12 patients, and 3 patients had positive margins after surgery. Two of the patients with positive margins underwent a second surgery. No

Table 1 Patient characteristics

Age, years (median, range)	55 (32–89)
Sex, n	
Male	6
Female	10
Prior surgery, n	
Yes	3
No	13
Prior radiation, n	
Yes	2
No	14
Prior chemotherapy, n	
Yes	3
No	13
Tumor grade, n	
High grade	13
Low grade	3
Tumor size, cm	
Median, range	6.7 (2.4–14)
>5	6
>5 < 10	6
>10	4
Tumor histology, n	
Mixofibrosarcoma	5
Liposarcoma	3
Synovial	3
Pleomorphic	2
Other	3

patient received additional radiation. The median tumor necrosis rate was 25% (range, 10%–95%). Wound complications occurred in 3 patients, with dehiscence at the site of a local recurrence requiring resection in 1 patient, a hematoma causing wound drainage requiring evacuation in 1 patient, flap necrosis requiring revision surgery in a 3rd patient. All 3 patients with wound complications had tumors in the lower extremities, including the thigh, knee, and ankle.

Late toxicity

The median follow-up time was 1719 days (range, 983–2327 days). Five patients developed late toxicity consisting of mild lymphedema in 3 patients, mild fibrosis in 1 patient, and equinus contracture that required tendon lengthening in 1 patient (patient's postoperative course

Table 2 Patient outcomes

Acute toxicity	n (%)
Skin grade 2	2
Skin grade 3	1
Wound complications	
Yes	3 (20)
No	12 (80)
Late toxicity	
Grade 1-2	4 (26.7)
Grade 4	1 (6.7)
Recurrence	
Distant	5 (33.3)
Local	1 (6.7)

was also complicated by flap necrosis requiring revision.) The only grade 4 late toxicity was this contracture. There was no apparent association between tumor size and late toxicity.

Oncologic outcomes

Tumor recurrences were noted in 6 patients, consisting of distant failure in 5 patients and local failure in 1 patient. The median time to distant failure was 248 days (range, 40-1161 days), and the site of distant failure included the lung (2 patients), bone (1 patient), and soft tissue (2 patients). The 1 local failure occurred in an elderly patient with a positive margin after initial resection, and she was unable to undergo repeat surgery secondary to other medical issues. The biopsy-proven recurrent tumor developed in the middle of the SBRT field, and was noted 150 days from completion of SBRT (100 days from surgery) at the same time as the patient developed wound dehiscence (Table 2).

Discussion

Preoperative radiation is a well-established standard treatment for STS, and recent studies using the latest in radiation technology with conventional fractionation have found local control rates of 93.2% to 88.6% and wound complication rates of 30.5%.⁴⁻⁵ We report similar results using SBRT in the preoperative treatment of STS. With a median follow up of 1719 days (4.7 years), we found a local recurrence in 1 of 15 patients (6.7%), wound complications in 3 of 15 patients (20%), and significant (grade ≥ 3) late toxicity requiring additional surgery in 1 of 15 patients (6.7%).

There are several advantages of SBRT in the setting of extremity STS. One of the obvious advantages is convenience. Because there is a significant reduction in the number of treatments (5 vs 25), logistics and patient-related costs with treatment are less burdensome. Similarly, by decreasing treatment time, SBRT could expedite the time to surgery and systemic therapy. SBRT could also result in decreased late toxicity because of the limited radiation exposure to normal tissue. Although the small numbers limit firm conclusions, we did not find size to be predictive for late toxicity because many sarcomas can be large, which is encouraging. Finally, the radioresistant nature of STS could theoretically be more effectively treated with a higher dose per fraction.

The majority of failures in our study were distant metastases (5 of 15 patients). This speaks to the aggressive nature of STS and the relative ineffectiveness of systemic treatment in STS. Three patients in this study had chemotherapy before SBRT, and of the patients with distant failure, 1 of 5 had received chemotherapy. We do not expect radiation technique to significantly change the rate of metastatic disease; however, if anything, we would expect SBRT to decrease distant failure rates indirectly by decreasing time to receiving systemic therapy.

Limitations of our study include relatively low numbers and being conducted at a single institution. Surgical resection was performed by 3 orthopedic oncology surgeons who use similar wound closure techniques; therefore, wound healing data may not be generalizable to other institutions. Our results are similar to those in other published reports.^{13,14} The University of California, Los Angeles¹³ used a slightly lower dose (30 Gy in 5 fractions) delivered daily (as opposed to every other day treatment in our study) using modern radiation techniques, but not SBRT. With a median follow-up time of 29 months, the researchers reported 32% wound complications and 16% late toxicity. Parsai et al¹⁴ reported early outcomes in 16 patients also treated with 5 fractions radiation (dose range, 27.5-40 Gy) and with a median follow up of 10.7 months, and found no local failure and 31% wound complications. Our series stands out as having a longer follow up than other publications, and thus able to better address local control and late toxicity rates.

Conclusion

Even when combining all studies (84 patients), the numbers are small, and these findings need to be further validated. A larger, multicenter, single-arm, phase II study would be helpful to overcome these limitations. However, based on the evidence presented herein, SBRT for the preoperative treatment of STS appears to be safe and effective.

References

1. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol*. 1998;16:197–203.
2. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomized trial. *Lancet*. 2002;359:2235–2241.
3. O'Sullivan B, Davis AM, Turcotte R, et al. Five-year results of a randomized phase III trial of pre-operative versus post-operative radiotherapy in extremity soft tissue sarcoma. *J Clin Oncol*. 2004;22:9007.
4. O'Sullivan B, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer*. 2013;119:1878–1884.
5. Wang D, Zhang Q, Eisenberg BL, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. *J Clin Oncol*. 2015;33:2231–2238.
6. Folkert MR, Singer S, Brennan MF, et al. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. *J Clin Oncol*. 2014;32:3236–3241.
7. Alektiar KM, Brennan MF, Healey JH, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol*. 2008;26:3440–3444.
8. Di Brina L, Fogliata A, Navarria P, et al. Adjuvant volumetric modulated arc therapy compared to 3D conformal radiation therapy for newly diagnosed soft tissue sarcoma of the extremities: outcome and toxicity evaluation. *Br J Radiol*. 2019;92:20190252.
9. Jacinto AA, Fede ABS, Salvajoli JV, et al. Hypofractionated radiotherapy to soft tissue sarcoma of extremities: Could it be an option? *Int J Radiat Oncol Biol Phys*. 2008;72:S506.
10. Soyfer V, Corn BW, Kollender Y, et al. Radiation therapy for palliation of sarcoma metastases: A unique and uniform hypofractionation experience. *Sarcoma*. 2010;2010: 927972.
11. Chang SD, Main W, Martin DP, et al. An analysis of the accuracy of the CyberKnife: A robotic frameless stereotactic radiosurgical system. *Neurosurgery*. 2003;52:140–146.
12. Kubicek GJ, LaCouture T, Kaden M, et al. Preoperative radiosurgery for soft tissue sarcoma. *Am J Clin Oncol*. 2018;41:86–89.
13. Kalbasi A, Kamrava M, Chu FI, et al. A phase II trial of 5-day neoadjuvant radiotherapy for patients with high-risk primary soft tissue sarcoma. *Clin Cancer Res*. 2020;26:1829–1836.
14. Parsai S, Lawrenz J, Kilpatrick S, et al. Early outcomes of preoperative five-fraction radiation therapy for soft tissue sarcoma followed by immediate surgical resection. *Adv Radiat Oncol*. 2020;5:1274–1279.