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Scientific Article

Early Outcomes of Preoperative 5-Fraction Radiation Therapy for Soft Tissue Sarcoma Followed by Immediate Surgical Resection

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Abstract

Purpose: There are limited data regarding the use of hypofractionated radiation therapy (RT) for soft tissue sarcoma. We report early oncologic outcomes and wound complications of patients undergoing preoperative hypofractionated (5 fraction) RT followed by immediate surgical resection.

Methods and Materials: An institutional review board–approved database of patients treated with preoperative RT for soft tissue sarcoma was queried. Patients treated with a hypofractionated dosing regimen followed by immediate (within 7 days) planned wide surgical resection were identified.

Results: Between 2016 and 2019, 16 patients met eligibility criteria. The median patient age was 64 years old (range, 33-88). Ten of the sarcomas were located in the lower extremity, 4 in the upper extremity, and 2 were located in the trunk. Four patients had metastatic disease at diagnosis. The majority of the patients received a total radiation dose of 30 Gy in 5 fractions (range, 27.5-40 Gy) on consecutive days. All patients were planned with intensity modulated radiation therapy or volumetric arc therapy. The median time to surgical resection after the completion of RT was 1 day (range, 0-7 days). The median time from initial biopsy results to completion of primary oncologic therapy was 20 days (range, 16-35). Ten patients achieved R0 resection, whereas the remaining 6 patients achieved R1 resection. Of the 13 patients assessed for local control, no patients developed local failure. Within the median follow-up time of 10.7 months (range, 1.7-33.2), 5 patients developed wound healing complications (31%), of which only 3 patients (19%) required return to the operating room.

Conclusions: Treatment of soft tissue sarcoma with preoperative hypofractionated RT followed by immediate resection resulted in a median of 20 days from biopsy results to completion of oncologic therapy. Early outcomes demonstrate favorable wound healing. Further prospective data with long-term follow-up is required to determine the oncologic outcomes and toxicity of hypofractionated preoperative RT.

Introduction

Soft tissue sarcomas are rare malignant tumors of mesenchymal origin. The mainstay of treatment is complete surgical resection and radiation therapy (RT),

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delivered either in the neoadjuvant or adjuvant setting. Local control and survival outcomes are similar when comparing neoadjuvant and adjuvant RT, though the toxicity profiles differ.[1,2] Preoperative radiation therapy is known to have a higher rate of wound healing complications, but improved extremity function due to less fibrosis of the periarticular soft tissues.[1] Conventional neoadjuvant RT regimens consist of 50 Gy in 25 fractions (fx) delivered over 5 weeks. When including a 3- to 6-week posttreatment period, time to surgical resection, and therefore completion of primary oncologic therapy, ranges between 8 to 11 weeks from the time RT is initiated.[1]

Hypofractionated RT, defined as >2.2 Gy delivered per fraction, has been shown to be efficacious in other cancer types, including breast,[3-5] rectal,[6] and prostate cancer.[7] Prior experiences of preoperative hypofractionated regimens have used 3.5 to 8 Gy per fraction.[8-12] Hypofractionated regimens considerably shorten the entire treatment package time. This allows for quicker time receiving adjuvant therapies, undergoing physical therapy, and reintroduction of the patient back into society with less time off work. In 2014, Kosela-Paterczyk et al reported on a prospective single-arm study of 272 soft tissue sarcoma patients treated with 25 Gray in 5 fractions followed by immediate (within 3-7 days) surgical resection.[12] Local control rate was lower than expected at 81% with a median follow-up of 35 months. However, the wound complication rate of 7% requiring reoperation was deemed favorable. Kalbasi et al reported on a single arm prospective study of patients with soft tissue sarcoma treated with 30 Gy in 5 fractions followed by delayed surgery (within 2-6 weeks).[13] The local control rates reported on 35 evaluable patients was 94.3% at 2 years. In this study, major wound complications occurred in 32%. At our institution, we have selectively used a high-dose preoperative hypofractionated regimen for patients with soft tissue sarcomas outside the abdomen and pelvis followed by immediate surgery. This represents a further advance combining the novel regimens previously published by Kosela-Paterczyk et al and Kalbasi et al.[12,13] Given the paucity of data (summarized in Table 1), we aimed to assess our early clinical, toxicity and histologic data of patients receiving hypofractionated RT followed by immediate surgical resection.

Methods and Materials

An institutional review board–approved database of patients treated with preoperative 5-fraction radiation regimens between 2016 and 2019 was queried. Patients with soft tissue sarcomas of the extremities or trunk treated with preoperative hypofractionated radiation therapy were included, whereas retroperitoneal sarcomas were excluded. The decision to use hypofractionated dosing regimen with immediate surgery was made as part of a multidisciplinary discussion and sarcoma tumor board. Patients with metastatic disease with long natural histories of disease, justifying aggressive local control or those with symptomatic primary tumors requiring local control and quick resumption of systemic therapy, were treated with short course radiation followed by immediate surgical resection. Patients with nonmetastatic disease were counseled regarding the current standard of care for preoperative long-course radiation therapy with conventional fractionation and delay to surgery. Patients consented to short course radiation therapy for various personal and logistical reasons. One patient treated with short course radiation therapy was an inmate at maximum security prison in a different city, who would not otherwise be able to receive preoperative radiation therapy. All patients were treated at a single institution. After surgical resection, patients were seen for surveillance every 3 to 6 months for the first 3 years. Surveillance imaging included a computed tomography (CT) chest without contrast and imaging of the primary tumor with magnetic resonance imaging (MRI).[14]

Radiation target delineation and treatment planning

All patients received hypofractionated preoperative radiation therapy over 5 fractions. Tumor volumes were generally designed as was done on RTOG 0630.[15] The planning CT was registered with preoperative MRI imaging performed before or at the time of simulation. The gross tumor volume was defined based on preoperative MRI with sequence based on histology. The CTV was drawn to respect anatomic barriers to tumor spread. The planning target volume was generated by adding 5 mm to the CTV. Daily image guidance with cone beam computed tomography was used. Both step and shoot intensity modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT) radiation techniques were allowed. We attempted to limit bone in proximity to planning target volume to V15 Gy <50% and to spare a strip of skin >2 cm to less than 10 Gy. We also consulted with our orthopedic surgeons to avoid hotspots in the skin where the surgical wound was planned. Acute and late radiation-related toxicities as were graded per the Common Terminology Criteria for Adverse Events v4.0 toxicity criteria.

Surgery and reconstruction

Surgical resection was performed by an orthopedic oncologic surgeon (L.N. and N.M.), 0 to 7 days after completion of the preoperative RT. Timing decisions were based upon patient preference and surgeon schedules. Wound healing complications were defined as

Table 1 Summary of other studies employing hypofractionated preoperative radiation therapy for soft tissue sarcoma

Author/institution	Year	No. of patients	Dose	Radiation technique	Time to surgery	Preoperative or concurrent chemotherapy	Local control	Complications requiring reoperation
Ryan et al[9]/ Oregon Health and Science University	2008	25	28 Gy/ 8 fx	3D conformal	9 wk	Yes	88% at 2 y	20%
MacDermed et al[8]/ University of Chicago	2010	34	28 Gy/8 fx	3D conformal	4-8 wk	Yes	89% at 5 y	17.2%
Kosela-Paterczyk et al[12]/ Maria Sklodowska Curie (Poland)	2014	272	25 Gy/5 fx	3D conformal	3-7 d	Yes	81% at 3 y	7%
Pennington et al[10]/ University of California, Los Angeles	2018	116	28 Gy/8 fx	3D conformal	1-2 wk	Yes	89% at 3 y	NA
Kubicek et al[11]/ Cooper University Hospital	2018	13	35 Gy-40 Gy/5 fx (every other d)	Radiosurgery with CyberKnife	4-8 wk	Optional	93% with median follow-up of 9.3 mo	0%
Kalbasi et al[13]/UCLA	2020	52	30 Gy/5 fx	IMRT (76%), 3D conformal (20%), or electrons (4%)	2-6 wk	None	94% at 2 y	32%

Abbreviations: 3D = 3-dimensional; fx = number of fractions; IMRT = intensity modulated radiation therapy; UCLA = University of California, Los Angeles.
The present study treated 16 patients with a mean dose of 30 Gy/5 fx on consecutive days followed by immediate surgical resection (within 7 days). All patients were treated with IMRT/volumetric arc therapy. Only patients with upfront metastatic disease were treated with preoperative chemotherapy. No local failures were observed within the follow-up time of 10.7 months. Complications requiring reoperation occurred in 19%.

previously described by O'Sullivan et al.[1] Major wound complications were those requiring return to the operating room, admission for intravenous antibiotics and wound packing >120 days, or aspiration of seroma.

Statistical analysis and definitions

Descriptive statistics were used to describe local failure, survival, toxicities, and wound complications of treatment. Local failure was assessed radiographically on surveillance MRI. Local failure was reported for patients who had >3 months of radiographic follow-up.

Results

Patient, tumor, and treatment characteristics

A total of 16 patients met the study eligibility criteria. A summary of the patient, tumor, and treatment characteristics is included in Table 2. Ten patients had diagnoses of soft tissue sarcomas of the upper extremity, 4 lower extremity, and the remaining 2 patients had trunk sarcomas. The majority of the patients had localized disease; however 4 patients had metastatic disease at diagnosis. Of the 4 patients who had metastatic disease at diagnosis, 1 patient received chemotherapy within a short interval before preoperative radiation therapy and surgical resection and 1 patient received chemotherapy within a short interval after radiation therapy and surgical resection. The details of these 4 patients with metastatic disease can be found in the Supplementary Patient Data. Chemotherapy was not administered neoadjuvantly or adjuvant in nonmetastatic patients. Most patients received 30 Gy in 5 fractions, with a dose range of 27.5 Gy to 40 Gy. The median time from completion of radiation to surgical resection was 1 day (range, 0-7). Median time from initial biopsy results to completion of primary oncologic therapy was 20 days (range, 16-35) as shown in Figure 1. The median time from initial biopsy to completion of primary oncologic therapy was 27 days (range, 21-38).

Oncologic outcomes

The median follow-up time was 10.7 months (range, 1.7-32.0). Within the follow-up time, 2 out of 16 patients died. Both of these patients had metastatic disease at the time of radiation and surgical resection, and continued to have distant progression, ultimately leading to demise. Within the follow-up time, no local failures were observed in the 13 patients with >3 months of radiologic follow-up. Gross total resections (R0) were achieved in 10 patients. In the remaining 6 patients, microscopically positive margins were identified. Five patients had planned marginal (R1) resections. One patient with myxofibrosarcoma had persistently positive margins outside of the radiation field after reresection. This patient

Table 2 Patient, tumor, and treatment characteristics

Age	Median 64 y, (range, 33-88)
Male	9
Female	7
Site	
Extremity	14
Upper extremity	4
Lower extremity	10
Trunk	2
Histology	
Dedifferentiated liposarcoma	1
CIC-rearranged sarcoma	1
Extraskeletal myxoid chondrosarcoma	1
Myxofibrosarcoma	4
Myxoid liposarcoma	3
Pleomorphic leiomyosarcoma	1
Synovial sarcoma	2
Undifferentiated pleomorphic/spindle cell sarcoma	3
Grade*	
Grade 2	8
Grade 3	3
Greatest tumor dimension on final pathology	
$\leq$5 cm	3
>5 cm and $\leq$10 cm	9
>10 cm and $\leq$15 cm	3
>15 cm	1
Metastatic at diagnosis	4
PTV size	Median 485 cm^3 (range, 56-4353)
Radiation technique	
Step and shoot IMRT	3
VMAT	16
Radiation dose	
27.5 Gy/5 fx	1
30 Gy/5 fx	14
40 Gy/5 fx	1
Prior unplanned excision with longitudinal incision	4
Wound closure	
Primary closure	13
Regional/pedicled flap	2†
Free flap	1
Skin graft	1†
Incisional wound vacuum use with surgery	13
Pathologic margin status	
R0	10
R1	6
R2	0

Abbreviations: fx = number of fractions; IMRT = intensity modulated radiation therapy; R0 = gross total resection; R1 = microscopically positive margins; R2 = macroscopically positive margins; volumetric arc therapy; VMAT = volumetric arc therapy.

* Grade not available for 5 patients.

† One patient underwent closure with a regional pedicle flap and a skin graft.

underwent postoperative reirradiation conventional fractionation to 66 Gy in 33 fractions.

Wound complications and toxicity

No acute or late grade 3 or higher radiation-related toxicities were observed, including lymphedema, fibrosis, joint stiffness, skin hyperpigmentation, atrophy, or pain. Major wound complications requiring reoperation occurred in 3 out of 16 patients (18.8%). Minor wound complications occurred in 2 out of 16 patients (12.5%). Major and minor wound complications included dehiscense, skin necrosis, and seroma. Figure 2 demonstrates representative images of wound complications.

Discussion

We present early oncologic and toxicity outcomes of treating soft tissue sarcomas with a 5-fraction preoperative hypofractionated radiation therapy courses followed by immediate surgical resection. This strategy significantly reduces the overall treatment time compared with conventional preoperative radiation therapy followed by delayed surgery, which generally ranges between 8 to 12 weeks. Our data demonstrate the median time from obtaining the biopsy results to surgical resection of the primary tumor, including preoperative radiation, was less than 3 weeks. In this way, the treatment package time was reduced by 5 to 9 weeks. This allows patients less absences from work and quicker resumption of activities of daily living. Additionally, for metastatic patients shortening the treatment course allows quicker resumption of systemic therapy.

With only 3 of 16 patients requiring reoperation for wound healing complications, our data demonstrate a rate comparable to that reported in the literature for standard fractionation radiation therapy.[16] In the National Cancer Institute of Canada study reported by O'Sullivan et al, acute wound complications were recorded in 35% of patients who received preoperative radiation therapy versus 17% in those that received postoperative radiation therapy. Of the patients who underwent preoperative radiation therapy, 16% of patients required reoperation owing to treatment complications.[1] This is comparable to our series, in which nearly 19% of patients required a reoperation. To date, most preoperative short course radiation therapy series have used 3-dimensional conformal techniques over more modern techniques. Older 3-dimensional conformal techniques, as were used in the original National Cancer Institute of Canada study of preoperative versus postoperative therapy, demanded larger target volumes without dose painting to avoid normal structures.[1] In our series, we uniquely used either step and shoot IMRT or volumetric arc therapy with image guidance for all patients. O'Sullivan et al

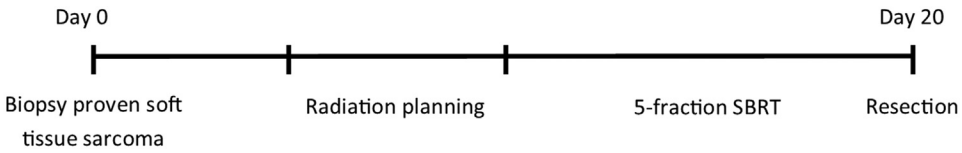

Figure 1 Treatment schema for preoperative hypofractionated radiation therapy followed by immediate surgical resection. The median time from initial biopsy results to surgical resection was 20 days. Surgical resection occurred within 7 days of completion of radiation therapy. *Abbreviation*: SBRT = stereotactic body radiation therapy.

demonstrated the use of IMRT with image guidance and that restricting radiation dose to future surgical skin flaps and bone reduced the risk of toxicity.[17] Wang et al (RTOG 0630) further used image guidance to reduce target volumes, which led to decreased late toxicities without an increase in the risk of recurrence.[15] The radiation techniques used in this study were modeled after RTOG 0630. Surgical efforts to decrease wound healing complications in this study included immediate surgical resection, layered closure when possible, use of deep drains to prevent seroma formation, and standard use of incisional wound negative pressure therapy techniques. No patients received concurrent chemotherapy with radiation therapy, and only 2 patients received chemotherapy within a short interval of radiation therapy (one patient received doxorubicin/temsirolimus 1 week before radiation, and 1 patient received gemcitabine/docetaxel 6 weeks after surgical resection). Therefore, the effects of chemotherapy on wound complications cannot be ascertained in this study.

Figure 2 Minor wound complication. This patient with skin necrosis, which ultimately led to cellulitis requiring short-term intravenous antibiotics, was characterized as a minor complication. This patient did not require reoperation.

Local control in this study is favorable, although our follow-up interval is too short to make definitive statements. There were no local failures observed within the follow-up period. Maturation of data are important to ensure longer term control remains favorable. A recent study of hypofractionated preoperative radiation (30 Gy in 5 fractions) followed by surgical resection within 2 to 6 weeks reported by Kalbasi et al demonstrated a 2-year local control rate of 94.3%.[8] This can be compared with the historical standard 5-year local control of 93%.[1] Table 2 summarizes the local control rates for prior experiences with hypofractionated preoperative radiation therapy. The largest reported series to date demonstrated an unexpectedly low 3-year local control rate of 81%.[12] This may be attributed to a low total radiation dose of 25 Gy in 5 fractions without chemotherapy. We chose to treat all patients with doses greater than 25 Gy (EQD2 = 40, calculated at alpha-beta ratio of 3) owing to the lower local control observed in that report. Most patients received radiation doses of 30 Gy in 5 fractions (EQD2 = 54, calculated at alpha-beta ratio of 3) before surgery with favorable toxicity profiles. In our series, immediate surgical resection was used in an effort to shorten the overall treatment course, similar to the treatment regimen published by Kosela-Paterczyk et al.[12]

New approaches in oncology are evaluated not only based on outcomes but value. Traditionally, preoperative radiation therapy consists of 25 fractions of radiation and postoperatively 30 to 33 fractions. A 5 fraction IMRT approach would provide great value compared with a 25 or 30 to 33 fractions of radiation delivered with IMRT. Data have demonstrated that 5 fractions of IMRT is reimbursed less than 15 fractions of 3-dimensional CRT so even if standard preoperative or postoperative radiation was delivered with 3-dimensional CRT compared with IMRT, a cost savings would be realized.[18] Finally, indirect costs that patients cover including missed work, travel and childcare are reduced with a shorter course of radiation therapy.

As a retrospective study design, this investigation has inherent limitations. The primary limitation is a selection bias of patients who have tumors felt to be amenable to hypofractionated radiation therapy and excluded cases at high-risk for toxicity (such as circumferential tumor close to bone). Longer follow-up and a larger cohort of patients is necessary to accurately determine the risk of severe wound complications, which may be underestimated in this study.

The short follow-up in this study may underestimate late toxicities such as lymphedema and soft tissue fibrosis which may have not yet manifested. Additional limitations include a small number of patients as well a heterogeneous group to stage, histology, location, and range of RT doses. Further prospective studies are required employing modern techniques of preoperative hypofractionated radiation therapy and immediate surgical resection.

Conclusions

Our use of hypofractionated preoperative RT for soft tissue sarcoma with immediate resection resulted in a median of 20 days from biopsy results to resection of the primary tumor, reducing the time from diagnosis to completion of primary oncologic therapy by nearly 3 months for these patients. Early outcomes demonstrate an acceptable rate of wound healing complications comparable to standard therapy. Further prospective data with long-term follow-up is required to determine the oncologic outcomes and toxicity of preoperative hypofractionated RT.

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Supplementary Patient Data

Supplementary material to this article can be found at https://doi.org/10.1016/j.adro.2020.06.024.

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