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Preliminary Results from a Prospective Study using Limited Margin Radiotherapy in Pediatric and Young Adult High Grade Non-Rhabdomyosarcoma Soft Tissue Sarcoma

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Abstract

Purpose—To demonstrate the safety and efficacy of limited margin radiotherapy in the local control of pediatric and young adult patients with high grade non-rhabdomyosarcoma soft tissue sarcoma (NRSTS).

Methods and Materials—Pediatric patients with high-grade NRSTS requiring radiation were treated on an IRB approved prospective institutional study of conformal / intensity modulated / interstitial brachytherapy using a 2 cm anatomically constrained margin.

Results—Thirty-two patients (median age 15.3 years, range 2–22 years) received adjuvant (27 patients) or definitive (5 patients) irradiation. With a median follow-up of 32 months, the 3-year cumulative incidence of local failure was 3.7% for patients irradiated after surgical resection. In total four patients experienced local failure; the mean dose to the volume of recurrence was $\geq 97\%$ of the prescribed dose.

Conclusions—Delivery of limited margin radiotherapy using external beam or brachytherapy provides a high rate of local tumor control without marginal failure. Further follow-up is required to determine if normal tissue effects are minimized using this approach.

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Conflicts of Interest Notification

No conflicts of interest exist.

Keywords

Soft-tissue sarcoma; Conformal; IMRT; Margin; Radiation

Introduction

The management of pediatric, adolescent and young adult patients (AYA) diagnosed with non-rhabdomyosarcoma soft tissue sarcoma has evolved from the adult paradigms of management (1–3). In current practice, the primary site of disease is managed with surgical resection, and radiation therapy is incorporated based on initial resectability, tumor grade and margin status (4–6). The indications for systemic chemotherapy are controversial; patients with unresectable disease and those with high-grade primary tumors > 5 cm are often treated pre- or post-operatively (7,8). When radiation therapy is indicated, pediatric patients are approached differently because of the desire to avoid late effects including impaired growth and development and potentially devastating life-long complications (9). Treatment guidelines in clinical trials for adult soft tissue sarcomas, particularly those of the extremity, have recommended target volume margins as large as 5 cm beyond the primary tumor or resection bed. They incorporate a large volume of normal tissue and often irradiate the surgical incision (10,11). When delivered in children, the adult approach using large treatment volumes and opposed tangential treatment beams places adjacent tissues at risk for late effects that include reduced bone growth, loss of joint function and soft tissue and muscle fibrosis (12–15). This has resulted in pediatric clinical trials that have lacked specific radiation treatment guidelines or avoided radiation resulting in outcome data that do not provide clear guidance as to the benefit or detriment of radiation therapy (16).

To address these issues, we designed a prospective trial to test the efficacy of focal limited margin radiation therapy delivered with conformal radiation, intensity modulated radiation or an interstitial brachytherapy approach. We report the initial results of this study for patients with high grade non-rhabdomyosarcoma soft tissue sarcoma, describing local disease control, patterns of failure and toxicity.

Methods and Materials

Pediatric and AYA patients with high grade non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) requiring radiation were treated on an IRB approved prospective phase II institutional study of limited margin radiation therapy. Eligibility included patients <25 years of age that required radiation therapy for management of their primary site of disease. Any primary site of involvement was allowed, and patients with metastatic disease were included. The primary objective of this clinical trial was to define the local tumor control rate for the NRSTS patient population with this radiotherapeutic approach. Secondary objectives, discussed in part in this manuscript, sought to define the early and late toxicity profile of this limited margin treatment approach related to the musculoskeletal system. Patients enrolled on this clinical trial were treated with radiation therapy, primarily in conjunction with surgical resection of the primary site of disease. Selection of patients necessitating preoperative, postoperative or definitive radiation was based on the presence of high grade sarcoma, positive microscopic margins and/or limited resectability (in cases receiving pre-operative or definitive irradiation). Degree of surgical resection was classified based on the description by Enneking and the pathologic margin status (17). Stage was assigned based on AJCC version 6 (18).

Treatment consisted of ICRU 50 target volumes generated based on CT and MR treatment planning datasets with MR data sets (typically obtained in the treatment position) co-registered to the CT to fully define target volumes (19). The gross tumor volume (GTV) was the post-

operative tumor bed or gross tumor constrained by barriers to tumor spread (bone, fascial planes) defined by the treating physician. A 2.0 cm clinical target volume (CTV) margin was added to the GTV, also anatomically constrained by barriers to tumor spread. The surgical incision was not targeted specifically. A site and patient specific planning target volume (PTV) was added that ranged from 0.4 cm to 1.0 cm. There was no PTV for brachytherapy cases. Radiation delivery was accomplished with conformal radiation therapy, intensity modulated radiation therapy, interstitial brachytherapy or a combination of these modalities. External beam radiation was delivered with 6 or 15 MV photons or megavoltage electrons while brachytherapy was delivered with low dose rate interstitial Iridium-192 seeds arranged in catheters and spaced 1.0 cm apart to deliver a homogenous dose. Specifics of external beam delivery techniques have been reported (20). Protocol specified total doses of radiation therapy were 55.8–63 Gy for postoperative radiation, 45–50.4 Gy for preoperative radiation and 70.2 Gy for definitive radiation, all delivered at 1.8 Gy per fraction. When interstitial brachytherapy was used alone, 45 Gy was prescribed.

Deviations from these dosing guidelines were made based on protection of adjacent normal tissues. Systemic therapy was at the discretion of the treating pediatric oncologist. In general, it was based on initial resectability and high risk features [large tumor size (>5 cm) and high histologic grade].

Follow-up for patients included a history, physical exam of the primary site of disease, MR imaging of the primary site, CT of the chest and other involved site imaging every 3 months for 2 years and then every 6 months until 5 years from protocol enrollment. Positron emission tomography (PET) with ^{18}F -fluorodeoxyglucose (FDG) was obtained at baseline, 6 months, 1 year and 2 years of follow-up. Toxicity was assessed weekly during radiation and at each follow-up visit according to the Common Toxicity Criteria version 2.0 (21).

Treatment failure was classified as local if the recurrence was within the PTV. Adjacent or marginal failures were also considered local for the purpose of defining the cumulative incidence. The cumulative incidence (CIN) of local failure was estimated by Gray's method and was defined as time to local failure with other events considered competing (22). The event free survival (EFS) was defined as the time to any event including local failure, distant failure, secondary malignancy or death prompting removal of the patient from the study. The Kaplan-Meier method was used to estimate event free survival (23).

Results

Patient Population

Thirty-two patients with high grade NRSTS were enrolled on this study from March 2003 through June 2007. The median age at the time of study enrollment was 15.3 years (range, 2.5–22.9). Fourteen patients were female, and 18 were male. The median follow-up of all patients remaining on study at the time of analysis was 32 months (range, 14–66 months). Tumor and treatment characteristics are shown in Table 1. Twenty-five patients received external beam radiation therapy, eight in conjunction with brachytherapy. Seven patient received brachytherapy without external beam radiation in conjunction with surgical resection. In some patient cases adjacent normal tissue tolerances limited delivery of the protocol specified prescription dose. The median cumulative dose delivered for patients receiving external beam radiation was 60 Gy (range, 41.4–70.4 Gy) in the post-operative setting, 45 Gy (range, 45–50.4 Gy) pre-operative and 50.4 Gy (range, 23.4–70.2 Gy) definitively. The median cumulative dose of post-operative brachytherapy delivered with external beam radiation therapy was 17.1 Gy (range, 13.8–20.0 Gy). Forty-five Gy was delivered in all patients treated with post-operative brachytherapy alone.

Local Failure

The 3-year cumulative incidence of local failure for the entire cohort was 12.5% (standard error (SE), 6%). Patients undergoing a marginal or complete resection with radiation therapy had a 3-year cumulative incidence of local failure of 3.7% (SE, 3.7%), while those patients receiving definitive radiation following biopsy had a 1-year cumulative incidence of local failure of 40% (SE, 28%, $p=0.0007$, figure 1). There were no significant differences in the incidence of local failure based on patients' primary tumor T-stage (T1 [≤ 5 cm] vs. T2 [>5 cm], $p=0.60$), overall stage (IIB vs. III vs. IV, $p=0.40$), or tumor location (extremity vs. head and neck vs. trunk, $p=0.37$). There also were no local failures in patients that had clear surgical margins, while the cumulative incidence of local failure for patients with positive surgical margins was 6.7% at 3 years ($p=0.37$). In patients undergoing resection, there was no difference in local control based on the addition of systemic therapy ($p=0.27$).

Event free survival

Event free survival for the entire cohort of 32 patients was 55.0% at 3 years. Patients that underwent resection fared significantly better than patients treated with definitive radiation having an EFS of 74.1% vs. 20.0% at 1 year and 65.2% vs. 0% at 3 years, respectively. The presence of metastatic disease significantly reduced EFS at 1-year (28.6% vs. 76.0%, $p<0.0001$). Delivery of systemic therapy in the context of resection resulted in no significant difference in EFS (3-year EFS, 68.1%) compared to management without systemic therapy (3-year EFS, 58.3%, $p=0.44$), although patients were not selected for systemic therapy uniformly.

Patterns of treatment failure

Four patients experienced a local treatment failure, three of which had only undergone biopsy and definitive radiation as local management. The remaining local failure occurred at the primary site in the wrist of a child with epitheloid sarcoma following marginal resection, 15 Gy interstitial brachytherapy and 45 Gy external beam radiation therapy. All local recurrences were within the high dose region of the patient's treatment plan based on co-registration of the recurrence imaging with the patients' radiation dosimetry. In all cases the mean dose in the volume of recurrence was 97% of the prescribed dose or greater. Ten patients had metastatic failure as their first recurrence, one of which was concurrent with a local failure. Metastatic failures were located in the lung/pleura (six) and regional lymph node, brain, bone and peritoneum (one each). The median times to local and distant failure were 9.9 months and 5.0 months, respectively.

Toxicity

In general, radiation therapy was well tolerated. The maximal toxicity noted for each patient by category is shown in Table 2. Two grade 4 toxicities were seen. In one patient skin necrosis occurred 7 months following treatment with 15 Gy interstitial brachytherapy and 45 Gy external beam radiation therapy. In the second patient a metatarsal fracture occurred 11 months following 63 Gy external beam radiation therapy delivered to the dorsum of the foot.

Discussion

We described the outcome for a prospectively treated well-defined cohort of patients managed with limited margin radiation therapy and either surgical resection or biopsy. Important to this study was the use of an anatomically constrained 2.0 cm clinical target volume margin designed to limit adjacent normal tissue dose. Despite the presence of reported adverse clinical factors including less than wide local surgical resections as well as primary tumor sites including the trunk and head and neck, the cumulative incidence of local failure in our patients undergoing resection was only 3.7% (24,25). Patterns of treatment failure indicate that sites of recurrence

were within the high dose treatment volume without marginal failure suggesting that in the pediatric population a 2.0 cm CTV margin is acceptable. It is important to note that on our study treatment planning was done with both CT and co-registered MR data sets typically obtained in the treatment position to fully define target volumes. This limited margin in the context of modern conformal or intensity modulated radiotherapy techniques reduces extra-target high dose volumes and may reduce long term treatment related effects. These findings are similar to the recently published adult experience of intensity modulated radiation in the extremity with a local control rate of 94%, employing similar radiation doses but larger treatment margins (26).

Despite radiation therapy treatment plans conformed to the primary tumor, 47% of patients were noted to have grade II or greater late soft tissue fibrosis, and 31% of patients were found to have moderate stiffness or reduction in joint range of motion related to radiation therapy. The further evolution and relation of these toxicities to the patients' dosimetry and clinical factors such as age at treatment will be explored in subsequent publications. Our experience with other radiation related late effects suggests that both clinical and dosimetric factors can be incorporated into a descriptive model providing a quantitative estimate of the toxicity (14). It will be important to identify whether these effects are related to high doses of radiation therapy directly adjacent to the clinical target volume or within the planning target volume or whether lower doses outside of the intended treatment region are responsible for these side effects.

Only the degree of surgical resection (biopsy vs. resection) was significant for an increased incidence of local failure. In the 12 patients undergoing a wide local excision achieving clear surgical margins, six had tumor less than 5.0 cm in the greatest dimension. Based on retrospective data in adults, this group of pediatric patients who have undergone a wide resection may be candidates for observation alone in the context of a clinical trial (as is being done in Children's Oncology Group trial ARST0332) (27–30). Patients with primary disease involving the trunk or head and neck did not experience an adverse local outcome despite the historic adverse prognosis that these features would predict (24,25). It is also interesting to note that in patients with metastatic disease there was no difference in local disease control. Despite these factors, the consistent targeting approach employed in this study resulted in high rates of local disease control.

Conclusions

A modern radiotherapeutic targeting and treatment approach yields excellent local disease control rates in pediatric and AYA patients diagnosed with non-rhabdomyosarcoma soft tissue sarcoma. This limited margin approach provides a benchmark for disease control and comparisons with future approaches including radiation dose reduction, volume reduction or application of new radiation technologies.

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Figure 1.
Cumulative incidence of local failure by degree of resection

Table 1

Patient Characteristics

	Number	Percent (%)
Histology		
Synovial cell sarcoma	6	19%
Malignant peripheral nerve sheath tumor	6	19%
Epitheloid sarcoma	4	12%
Mesenchymal chondrosarcoma	3	9%
Other high grade sarcoma	13	41%
Tumor Depth		
Superficial	1	3%
Deep	31	97%
Tumor Size		
≤ 5 cm	12	38%
>5 cm to ≤10 cm	11	34%
> 10 cm	9	28%
T Stage		
T1A	1	3%
T1B	11	34%
T2B	20	63%
AJCC Overall Stage		
IIB	12	37%
III	13	41%
IV	7	22%
Tumor Location		
Extremity	17	53%
Head & neck	3	9%
Trunk	12	38%
Degree of Resection		
Biopsy	5	16%
Intralesional excision	1	3%
Marginal	14	44%
Wide local excision	12	37%
Chemotherapy		
No	12	38%
Yes	20	62%
Doxorubicin / Ifosfamide based	11	55%
Other	9	45%
Radiation Therapy Regimen		
Post-operative radiation	24	75%

	Number	Percent (%)
Pre-operative radiation	3	9%
Definitive radiation	5	16%

Table 2

Adverse Events Categorized by Grade according to NCI-CTC (version 2.0)

	Grade			
	I	II	III	IV
Early				
Dermatitis	8	13	1	2
Pain	3	4	0	0
Muscle weakness	1	1	0	0
Myositis	4	0	0	0
Wound infection / Dehiscence	1	1	0	0
Early effects total	17	19	1	2
Late				
Joint function	7	10	0	0
Skin atrophy / Injury	15	8	0	1
Fibrosis	7	14	1	0
Bone growth / Injury	2	1	0	1
Lung	2	0	0	0
Late effects total	33	33	1	2