

FAST NEUTRON RADIOTHERAPY FOR SOFT TISSUE AND CARTILAGINOUS SARCOMAS AT HIGH RISK FOR LOCAL RECURRENCE

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Purpose: The practice policy at the University of Washington has been to employ fast neutron radiotherapy for soft tissue sarcoma lesions with prognostic features predictive for poor local control. These include gross residual disease/inoperable disease, recurrent disease, and contaminated surgical margins. Cartilaginous sarcomas have also been included in this high-risk group. This report updates and expands our previously described experience with this approach.

Methods and Materials: Eighty-nine soft tissue sarcoma lesions in 72 patients were treated with neutron radiotherapy in our department between 1984 and 1996. Six patients, each with solitary lesions, were excluded from analysis due to lack of follow-up. Seventy-three percent were treated with fast neutron radiation alone, the rest with a combination of neutrons and photons. Median neutron dose was 18.3 nGy (range 4.8–22). Forty-two patients with solitary lesions were treated with curative intent. Thirty-one patients (including 7 previously treated with neutrons) with 41 lesions were treated with the goal of local palliation. Tumors were predominantly located in the extremity and torso. Thirty of 35 (85%) of curative group patients treated postoperatively had close or positive surgical margins. Thirty-four (82%) lesions treated for palliation were unresectable. Thirty-five patients (53%) were treated at the time of recurrence. Median tumor size at initial presentation was 8.0 cm (range 0.6–29), median treated gross disease size was 5.0 cm (range 1–22), and 46/69 evaluable lesions (67%) were judged to be of intermediate to high histologic grade. Fourteen patients (21%) had chondrosarcomas.

Results: Median follow-up was 6 months (range 2–47) and 38 months (range 2–175) for the palliative and curative groups, respectively. Kaplan-Meier estimates were obtained for probability of local relapse-free survival (68%), distant disease-free survival (59%), cause-specific survival (68%), and overall survival (66%) at 4 years for the curatively treated group. For the palliatively treated group, estimated local relapse-free survival at 1 year was 62%. Log-rank analysis of the curative group revealed recurrent disease to be the only risk factor predictive for significantly worse local and distant disease-free survival. Intermediate-/high-grade histology was predictive for inferior overall survival. Effective clinical response was documented for 21/27 (78%) lesions treated palliatively. Ten patients (15%) experienced serious chronic radiation-related complications. All of these patients had clinical situations requiring delivery of high neutron doses and/or large radiotherapy fields.

Conclusion: Fast neutron radiotherapy is locally effective for soft tissue and cartilaginous sarcomas having well-recognized high-risk features. Results in the palliative setting appear to be particularly encouraging, with neutrons frequently providing significant symptomatic response for gross disease, with minimal serious chronic sequelae. Fast neutron radiotherapy should be considered in patients at high risk for local recurrence in both the curative and palliative settings. © 2001 Elsevier Science Inc.

Sarcoma, Neutrons, Radiotherapy, Local control, Palliation.

INTRODUCTION

Radiotherapy has played a pivotal role in the local therapy of soft tissue sarcomas, enabling orthopedic surgeons to safely preserve vessels, nerves, joints, and extremities. The addition of pre- or postoperative radiation significantly improves upon the results obtained with conservative surgery alone, decreasing local recurrence rates from 50% to ap-

proximately 10%, while still providing good functional results (1–5).

However, the success of conservation therapy is markedly less for patients with contaminated surgical margins following resection. Institutional series, for example, have consistently shown local failure rates ranging from approximately 20% up to as high as 38% in patients with positive

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Presented in abstract format at the 86th Annual Meeting and Scientific Session of the Radiological Society of North America, Chicago, IL, November 2000.

Accepted for publication 13 December 2000.

resection margins (6, 7). Recurrent sarcomas, as well, are difficult to control locally. Recurrent lesions frequently share similar high-risk features seen in their preceding index lesions (such as deep-seated location, bulky size, and high histologic grade). Recently published reports from M. D. Anderson reveal local control rates following salvage resection and irradiation to be in the range of 65% for recurrent tumors (8, 9).

The consequences of gross *de novo* disease or post-surgical residuum are even more significant; modern institutional experiences with conventional photon radiation alone for gross disease have confirmed only a modest 20–33% local control success rate (10, 11). This is discouraging not only for patients with unresectable primary disease, but also for patients requiring palliation for locally recurrent or end-stage disease, for whom aggressive surgery would be unacceptably morbid.

An alternative to conventional photon radiation is fast neutron radiotherapy. Neutrons are a high linear energy transfer radiation, which provide several radiobiological advantages over photon radiation. Neutrons are able to (a) efficiently kill cells in hypoxic conditions, (b) inflict irreparable cellular damage, and (c) produce consistent toxicity throughout the cellular reproductive cycle (12). These factors are specifically amenable to sarcomas, which frequently present as large, rapidly progressing masses with hypoxic, centrally necrotic cores. Clinical experience has confirmed these advantages; recently published reports from Europe detail local control rates of approximately 50% for macroscopic or bulky disease treated definitively with neutrons (13, 14). The most recent publication of our experience at the University of Washington reported a 71% local control rate. However, this was limited to a study population of 21 patients (12).

Since this earlier report, we have followed a uniform practice policy in our department to substitute fast neutron radiotherapy for standard photon radiation for patients with prognostic features most predictive for poor local control. These include the presence of gross residual or inoperable disease, recurrent disease, positive/contaminated surgical margins, and large tumor size at initial presentation. We have also utilized fast neutrons as primary or adjuvant therapy for cartilaginous sarcomas, which historically have been considered a radioresistant subtype (15, 16). This report updates and expands our previously described experience, with emphasis placed on respective results in the curative and palliative settings.

METHODS AND MATERIALS

Eighty-nine soft tissue and cartilaginous sarcoma lesions in 72 consecutive patients were treated in our department with fast neutron radiotherapy between 1984 and 1996. Retrospective analysis of these patients' medical center records was conducted following approval by the University of Washington institutional review board. Six patients, each with solitary lesions, were excluded from analysis due to

lack of follow-up. The University of Washington Sarcoma Service evaluated all patients in a multidisciplinary fashion. Pretreatment studies included baseline computerized tomography (CT) and/or magnetic resonance imaging (MRI) of the primary tumor site. Patients were routinely evaluated for occult pulmonary metastases via chest CT scanning. Surgical resection, if performed, was conducted by the orthopedic surgical service at the University of Washington Medical Center (UWMC). This included re-exploration and complete surgical bed resection for patients who received incisional biopsies at outside referring institutions. All tissue biopsies at our institution were performed via excisional technique. Limb sparing was the goal for all definitive resections of lesions located in the extremities and peripheral torso. Patients were considered inoperable if disease was too bulky or was too closely invested to critical normal structures such as nerve roots, vessels, or viscera, to allow for an acceptable functional result postoperatively. All studied patients had formal pathologic evaluation of their disease performed at UWMC, with histologic grading reported as per the French Federation Cancer Centers Sarcoma Group grading system (17); however, for the purpose of this report, histologic grade and surgical margin status were considered unevaluable if diagnostic uncertainty existed in the medical records.

Patients were referred to our department for specific consideration of curative neutron radiotherapy if they had localized gross residual or inoperable disease, recurrent disease, positive/contaminated surgical margins, or large tumor size at initial presentation. Five patients with limited metastatic pulmonary or i.p. disease that had been surgically resected were treated with curative intent; these patients were included in the analysis of the curative patient cohort on the basis of the intention of their treatment. All patients referred for palliative treatment had gross disease unamenable to surgery and/or end-stage metastatic disease.

The neutron radiotherapy was delivered using the University of Washington cyclotron, as previously described by Risler *et al.* (18). The cyclotron utilizes a 50-MeV proton on beryllium reaction, has an isocentric gantry, and has customized beam shaping provided by continuously variable multileaf collimation. Three-dimensional (3D) computerized treatment planning was universally employed. Gamma-ray contamination within the neutron beam was included in all calculated doses. Treatments were administered 4 days a week, with all fields treated daily. The initial radiation fields had generous 5–7-cm margins around a clinical tumor volume determined by pre- and postoperative CT and MRI. For patients treated postoperatively, surgical drain and incisional sites were included within the initial treatment volume. Hematoma cavities, if present pre- or postoperatively, received comprehensive treatment coverage. After delivery of approximately 10 nGy, a shrinking field technique was used to deliver a 6–12-nGy boost to areas of direct disease involvement, with approximately 3-cm circumferential

margins. A total treatment dose of at least 18 nGy was delivered for gross disease/positive surgical margins, unless the treatment was constrained by the proximity of dose-limiting structures (e.g., spinal cord, bowel). For extremity lesions, a strip of soft tissue and skin was excluded from all treatment fields to minimize risk for post-radiotherapy limb edema. Although the majority of patients were treated with fast neutron radiation alone, 13 (19.6%) received a combination of neutrons and external beam photon radiation, and 3 (4.5%) with recurrent disease received neutrons and brachytherapy. Median neutron dose was 18.3 nGy (range 4.8–22). Median photon dose was 32.5 Gy (range 10–60).

Patient characteristics are summarized in Table 1. Forty-two patients with solitary lesions were treated with curative intent. Median follow-up for these patients was 38 months (range 2–175). None of these patients had received prior radiotherapy. Thirty-one patients with 41 discrete lesions were treated with the goal of local palliation. Median follow-up for this patient cohort was 6 months (range 2–47). Seven of these patients had been treated with neutrons with curative intent previously. Seven palliative patients had multiple lesions irradiated (range 2–4), and 20 (48%) of the lesions treated palliatively were metastases.

Twenty-two of 42 patients treated curatively (53%) received chemotherapy as a component of treatment. Specific regimens administered were as follows: adriamycin/cisplatin, 12 cases; adriamycin/DTIC, 5 cases; DTIC/vincristine/cytosin, 1 case; ifosfamide/mesna, 1 case; intra-arterial cisplatin-based therapy, 3 cases. Thirty-two of 41 (78%) lesions treated with palliative neutron therapy had received systemic therapy during their treatment course for either cure or salvage. Specific combinations of agents were as follows: adriamycin alone, 5 cases; adriamycin/cisplatin, 5 cases; adriamycin/cytosin, 2 cases; adriamycin/DTIC, 8 cases; adriamycin/ifosfamide/mesna, 5 cases; ifosfamide/mesna, 2 cases; intra-arterial cisplatin-based therapy, 5 cases.

Patients underwent routine follow-up evaluations at 3–6-month intervals, consisting of history and physical examination, and surveillance MRI and CT scans of the primary tumor site. Serial chest CT scans were performed every 3 months for patients with nonspecific abnormalities seen on baseline studies. Otherwise, patients received chest X-rays at least bi-annually. Patients treated palliatively were followed on an individualized basis, and were typically seen more frequently to assist with supportive care. The palliative efficacy of neutron radiotherapy was evaluated retrospectively via review of patient hospital charts. Analysis was restricted to patients treated for gross residual disease, and who survived and were followed for ≥ 3 months. A positive response was defined as documentation of subjective local pain relief and symptom control and/or a $\geq 25\%$ decrease in tumor dimensions by clinical or radiographic examination. This response had to be of at least 1 month's duration to be considered positive.

Local relapse-free survival (LRFS), distant disease-free survival (DDFS), disease-specific survival (DSS), and over-

Table 1. Patient characteristics

Characteristic	No.	
	Curative cohort	Palliative cohort
Patients	42	31
Lesions	42	41
Age (years)		
Median (range)	51 (19–81)	55 (22–75)
Gender (M/F)	24/18	18/13
Location of tumor		
Extremity	15	12
Torso	15	19
Head and neck	8	2
Retroperitoneum	2	5
Viscera	2	3
Tumor size (cm)		
Median (range)	7.5 (0.6–29)	7.0 (3–22)
5 cm or larger (%)	28 (67)	32 (78)
10 cm or larger (%)	16 (38)	16 (39)
Histology		
Liposarcoma	11	4
Leiomyosarcoma	6	5
Fibrosarcoma	1	8
Spindle cell sarcoma	5	5
Synovial cell sarcoma	4	2
Malignant fibrohistiocytoma	3	1
Neural sheath sarcoma	0	4
Angiosarcoma	1	4
Other soft tissue	3	1
Chondrosarcoma	8	7
Histologic grade		
Low	14	9
Intermediate	9	4
High	14	19
Unclassified	4	9
Surgical margins		
Negative	5	2
Close (< 1 mm)	11	0
Positive	19	3
Unevaluable	0	2
Surgically unresectable (%)	7 (17)	34 (82)
Gross disease		
Number treated (%)	17 (40)	35 (82)
Median size in cm (range)	5 (1–15)	7 (3–22)
Metastases treated (%)	–	20 (48)
Bone	–	9
Lung	–	6
Soft tissue/viscera	–	5
Recurrent disease (%)	9 (21)	35 (85)
Systemic therapy		
Yes (%)	22 (53)	32 (78)

all survival (OS) were estimated by the Kaplan-Meier method (19). Local relapse was defined as any disease recurrence or progression within the radiotherapy treatment fields. Survival outcome differences were analyzed by the log-rank test for the following patient and treatment-related variables: surgical margin status (positive vs. negative/close margins), presence of gross disease, pathologic disease grade (low vs. intermediate/high), tumor size at presentation (≥ 5 cm vs. < 5 cm), presence of unresectable disease, chondrosarcoma histology, recurrent disease, and administration of systemic treatment.

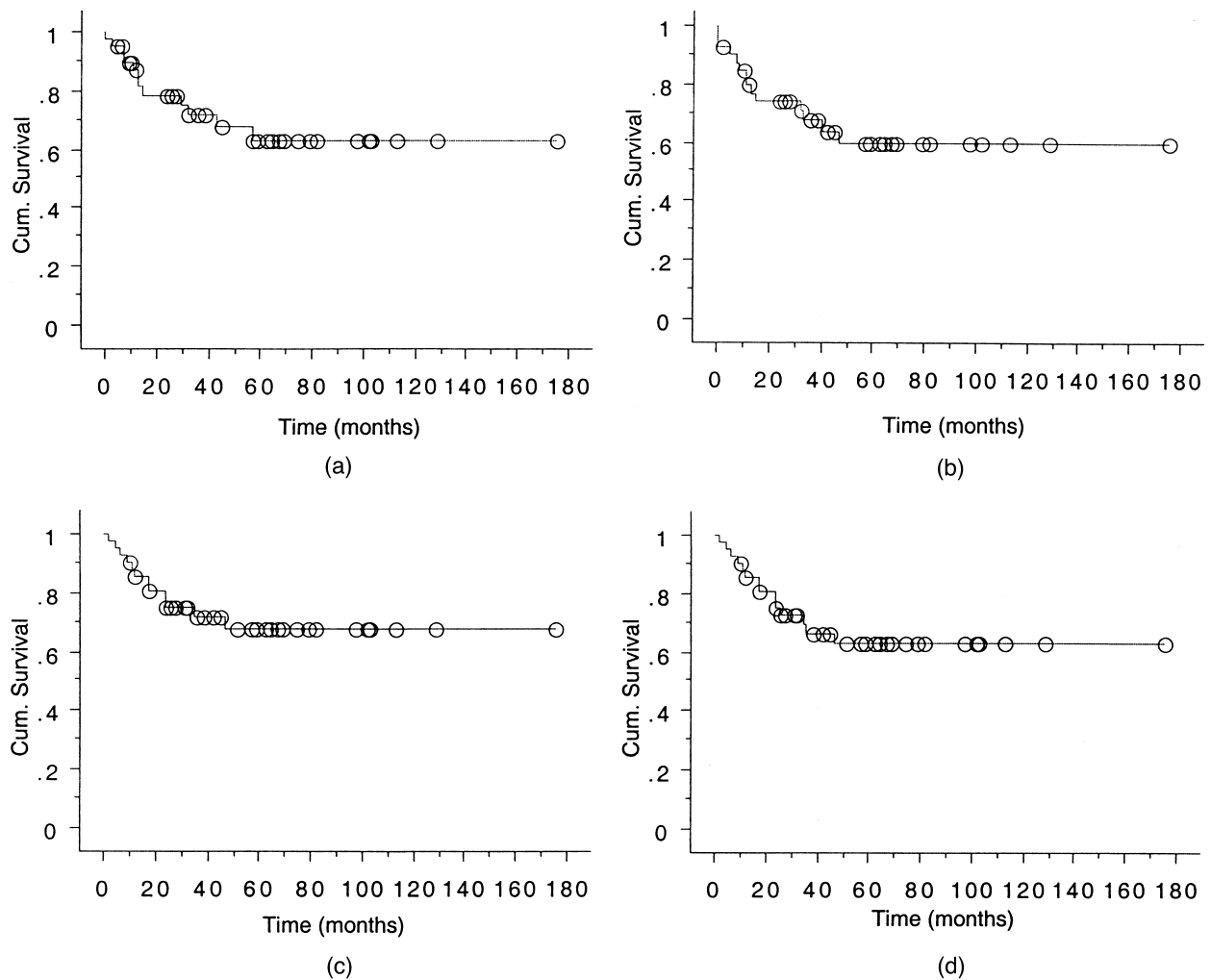


Fig. 1. Kaplan-Meier estimated LRFS (a), DDFS (b), DSS (c), and OS (d) for curatively treated study patients. Circles represent censored events.

RESULTS

Figures 1a–d show Kaplan-Meier estimated LRFS, DDFS, DSS, and OS for the curatively treated study cohorts. Univariate log-rank analysis revealed that recurrent disease predicted for poor local control (35.7% vs. 78.7% for primary disease at 38 months, $p = 0.045$) and distant disease-free control (31.3% vs. 75.6% for primary disease at 38 months, $p = 0.02$) [Figs. 2a and b], without significantly affecting DSS ($p = 0.12$) or OS ($p = 0.19$). No other study variable significantly affected local or distant disease control; however, there was a strong trend toward decreased distant disease-free survival when high-/intermediate-grade patients were compared to patients with low-grade histology ($p = 0.055$). Intermediate-/high-grade histology negatively impacted upon OS (59% vs. 91.7% for low grade, $p = 0.042$) (Fig. 3).

LRFS for the palliative treatment group is shown in Fig. 4. Local control for those patients surviving 1 year was 62%.

Seventeen patients in the curative cohort were treated for gross disease. Estimated 4-year LRFS was 61%, as opposed

to 69% for the 25 patients with negative or microscopically positive surgical margins ($p = 0.76$ by log-rank). Thirty-five gross lesions treated in the palliative group had an estimated LRFS of 67% at 1 year. For the 6 submacroscopic lesions treated in the palliative group, estimated LRFS was 100% at 8 months.

For both the curative and palliative treatment groups, administration of systemic therapy did not impact significantly upon any of the studied outcome parameters.

Effective palliative response, as defined by documentation of subjective local pain relief and symptom control and/or a $\geq 25\%$ decrease in tumor dimensions by clinical or radiographic examination, was seen in 21/27 (78%) of evaluable lesions.

Ten patients (15%) experienced serious chronic radiation-related complications. Patient and treatment-related characteristics of these subjects are summarized in Table 2. Median treatment dose was 19.8 Gy (range 15–22) and median treatment port area was 320 cm² (range 80–617.5). Only 1 of these patients (#10) had been treated with palliative intent; this patient's morbidity was limited to chronic

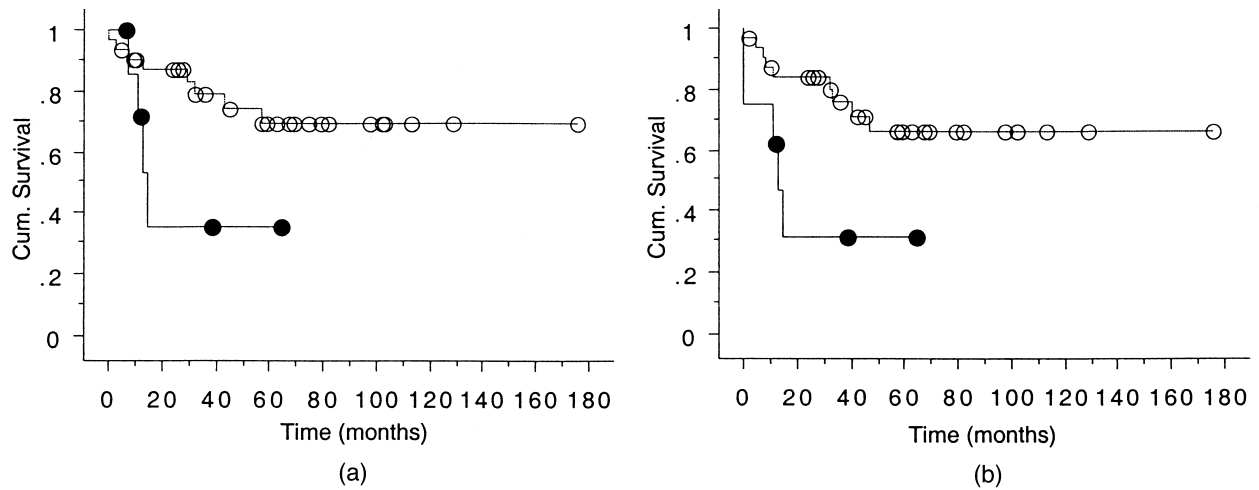


Fig. 2. Kaplan-Meier estimated LRFS (a) and DDFS (b) for primary (open circles) and recurrent (filled circles) disease treated in the curative study cohort. $p = 0.045$ and 0.02 , respectively, by log-rank analysis. Circles represent censored events.

sciatic neuropathy, and followed delivery of 20.4 nGy for 10-cm gross disease. Other specific complications included 3 cases of soft tissue necrosis, 2 cases of osteoradionecrosis, 2 cases of severe fibrosis (range of motion limitation and/or pain), 1 case of tibular-fibular fracture, 1 case of radiation colitis requiring colectomy, 1 case of constrictive pericarditis requiring pericardial stripping (in a patient who had previously received adriamycin-based chemotherapy), and 1 case of fatal radiation pneumonitis. Acute radiation morbidity was typically limited to skin/soft tissue reactions and radiation enteritis; no > 3 RTOG-defined acute reactions were reported.

DISCUSSION

Our institution has previously demonstrated a 71% (15/21 patients) local control rate for gross soft tissue lesions

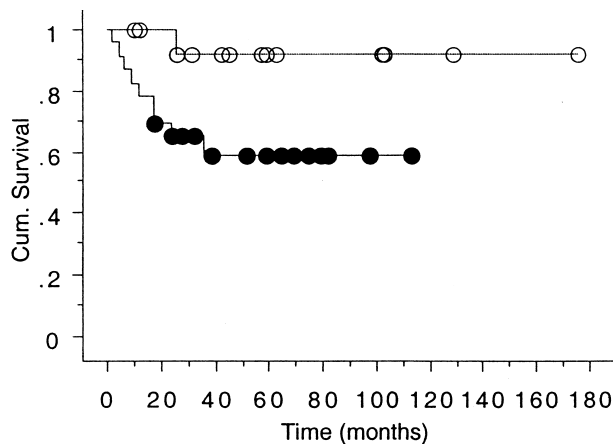


Fig. 3. Impact of intermediate-/high-grade histology (filled circles) vs. low grade histology (open circles) on Kaplan-Meier estimated OS in the curatively treated study cohort. $p = 0.04$ by log-rank analysis. Circles represent censored events.

treated with neutrons alone (12). This current series corroborates these early findings and compares favorably to data previously reported in the literature, summarized in Table 3. Of special note is the recent review by Schwarz *et al.*, which provides an extensive overview of the European neutron sarcoma experience encompassing the treatment of 1,171 patients at 11 referral centers between 1975 and 1995 (13). This review confirmed a published range of 21–60% (average of 50%) local control for patients treated definitively or postoperatively with neutrons for gross macroscopic disease. In our series, neutron radiotherapy yielded correspondingly good local control rates for gross disease in both the curative (61%) and palliative (67%) settings. Local control in our patients with no residual disease or microscopic disease residuum was consistent with European institutional results (65–94% in the Schwarz *et al.* review, as opposed to 69% in our series).

The local control benefits of neutron radiation were striking in our palliative patient population. Estimated LRFS

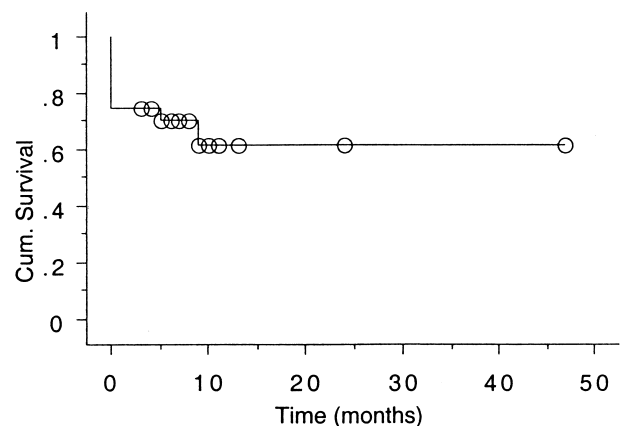


Fig. 4. Kaplan-Meier estimated LRFS for palliatively treated study patients. Circles represent censored events.

Table 2. Serious treatment-related morbidity

Patient	Location	Histology	Tumor size (cm)	Risk factors	Chemo?	Neutron dose (Gy)	XRT given Postop	Initial field size (cm)	Complications
1	L thigh	Lipo	20	PM	No	18.4	Yes	14 × 24.5	STN requiring amputation
2	Mediast.	Chondro	20	RD, PM	No	22	Yes	N/A	Sternum ORN
3	R Buttock	Chondro	29	PM	No	19.2	Yes	16.5 × 32.5	STN requiring graft
4	Tongue	Lipo	1.5	PM	No	22	Yes	10 × 8	ORN, STN
5	Mediast.	Spindle cell	5.5	GD	Adria/ CDDP	15	Yes	19 × 32.5	Pericarditis requiring stripping
6	Mediast.	Angiosarc	3	GD	No	18.4	No	N/A	Fatal pneumonitis
7	Lumbar back	Lipo	8	GD	No	20.4	No	14.5 × 20.5	Colitis requiring colectomy
8	R thigh	Lipo	9	GD	IA CDDP	16.5 + 19.8 photon	Yes	16 × 40	Fractures, fibrosis
9	L ankle	Synovial	2.5	RD	No	21.8	Yes	16.5 × 7	Fibrosis requiring amputation
10	R thigh	Leiomyo	11.5	RD, GD	Adria/ CDDP	20.4	No	16.5 × 12.5	Severe sciatica

Abbreviations: PM = positive margin; RD = residual disease; GD = gross disease; STN = soft tissue necrosis; ORN = osteoradio-necrosis; IA CDDP = intra-arterial cisplatin; Mediast. = mediastinum; Leiomyo = leiomyosarcoma; N/A not available.

was greater than 60% for patients surviving 1 year or longer. Even more significantly, effective palliation appeared to be the norm for this treatment group, occurring in almost 80% of patients with gross disease who survived and could be followed for at least 3 months.

In comparing our findings to the existent literature, a crucial point to consider is the dose of neutron therapy delivered. Our study group received a median dose of 18.3 nGy. More than 647 (55%) patients in the European series received less than 16 nGy of therapy. Patients treated in the

Table 3. Literature review

Author/Institution	No. of patients	Mean F/U (mo.)	Tumor status	Neutron dose (Gy)	Neutron generating reaction	Results	RTOG grade ≥ 3 chronic morbidity
Duncan, <i>et al.</i>	4	> 24	NR	13.8–18.3	d(15)+Be	75% LC	50% RTOG Gr 3/4
Edinburg (24)	12	> 24	GD	15.6	d(16)+Be	41.7% LC	30% RTOG grade 4
Pickering <i>et al.</i>	16	> 24	NR	23.2	d(65)+Be	94% LC at 5 yr.	16% (31% for fields > 20-cm diameter)
Hammersmith (22)	50	30.7	GD	13.6–16	dT	52% LC at 5 yr.	54% in patients receiving > 13.4 Gy
Richard <i>et al.</i>	47	NS	NR	6.3 boost	d(14)+Be	91.5% LC, 70% OS	7% RTOG Gr 3/4
Louvain-la-Neuve (23)	28	(absolute)	GD	16.8	p(66)+Be	18% LC, 68% OS	28% RTOG Gr 3/4
Hubener, <i>et al.</i>	63	> 6	NR/PM/GD	18–20.4		18% LC	26% RTOG grade 4
Hamburg (25)	23	60	NR/PM	6–12	d(13.5)+Be	80% LC, 69% DFS	14% ulceration, 9% colitis, 9% proctitis
Schmitt, <i>et al.</i>	94	(median)	GD	See text	See text	56% LC, 26% DFS	11% (half of cases involved fibrosis)
Dusseldorf (26)	24	20–45	GD	See text	See text	46% CR	7–18% for low dose; up to 59% for large fields
Stannard, <i>et al.</i> / Cape Town (27)	221	NS	NR	18	d(50)+Be	65% LC	9/42 (21%)
Steingraber, <i>et al.</i>	61	44	GD	14.1	dT	55% LC	Grade ≥ 4
Berlin-Buch (28)	61	(median)	GD	14.1	dT	51.8% LC, 52.5% OS at 5 yr.	1/35 (3%) Grade ≤ 4
Schonekaes, <i>et al.</i>	225	20–45	NR/PM	See text	See text	65–94% LC	
Munster (14)	429	(median)	GD	18.3	"	21–60% LC	
Schwarz, <i>et al.</i>	25	38	NR/PM	18	d(50)+Be	69% LC	
European Review (13)	17	(median)	GD	18.3	"	61% LC (at 4 yr.)	
Current series (Curative)	35 lesions	6	GD	18.3	"	67% LC (at 1 yr.)	
Current series (Palliative)		(median)					

Abbreviations: NR = no residual disease; PM = positive margin; GD = gross disease; LC = local control; OS = overall survival; DFS = disease-free survival; CR = complete response; NS = not stated.

Note: The nomenclature for each facility's respective neutron beam generating reaction denotes the peak energy in MeV of the accelerated particle (p = proton, d = deuteron) and the target material (Be = Beryllium). dT = deuterium-tritium generator.

Table 4. Patients treated with “neutron boost”

Patient	Neutron dose (Gy)	Photon dose (Gy)	CTX?	Location/Histology	Tumor size (cm)	Risk factors	Local control (mo. f/u)	Overall survival (mo. f/u)
A	4.8	41.1	Yes	RP/Lipo	> 10	PM, Grade 3	No (47)	Yes (51)
B	4.8	45	Yes	Torso/MFH	6	CM	Yes (69)	Yes (69)
C	7.0	29	Yes	Torso/Fibro	10	GD	No (43)	No (47)

CTX = chemotherapy; RP = retroperitoneum; PM = positive margin; MFH = malignant fibrous histiocytoma; CM = close margin; GD = gross disease.

European series frequently received neutrons as a “boost” treatment, many times limited to 4–6 nGy. Neutron boosts were typically given to patients with clean or microscopically positive margins. We treated three patients in this manner (summarized in Table 4). Two of these 3 patients failed locally. It is reasonable to conclude that aggressive administration of neutron radiation is necessary for optimal local control.

It is also important to highlight technical differences in the delivery of neutron therapy between institutions. The University of Washington cyclotron delivers 50.5-MeV fast neutrons, with tissue penetrance comparable to that of 8-MV photons. Several of the institutions included in the Schwarz *et al.* review (Hamburg/Eppendorf, Essen, and Heidelberg) used low-energy neutron cyclotrons or dT (deuterium-tritium)-generators. Treatment beams from these systems have high biologic efficacy (20), but are suboptimal for treating deep-seated tumors. Six hundred eighty-seven patients (59%) included in the European review were treated at these facilities. Optimal beam quality, therefore, may also explain why our local control rates for gross disease matched or exceeded the best results reported in the European series.

In our curative patient population, neutrons provided a 68% local relapse-free survival at 4 years, comparable to results described in our previous report. Significantly, neutrons were able to provide this efficacy for patients with the most worrisome of high-risk features, such as the presence of contaminated surgical margins or unresectable gross disease. Standard photon radiotherapy fails locally in up to 70–80% of such cases. It should be noted, however, that patients with recurrent disease in our series did not share the local control benefits seen in other high-risk groups following curative administration of neutrons. This cannot be easily explained, given that these patients did not have prior radiotherapy exposure and did not have unique treatment or patient-related characteristics. However, recurrent disease has a tendency to be locally aggressive and frequently arises from high-risk primary disease.

Disease-specific and overall survival in our curative pa-

tient population was comparable to previously published data for patients with Stage II/III disease (50–75% survival at 4 years) (21). Not surprisingly, patients with higher histologic grade disease had a strong tendency toward inferior distant disease control and, consequently, inferior overall survival despite effective local control. The addition of systemic therapy did not impact upon these findings. Patients with low histologic grade disease had excellent long-term survival of greater than 90%.

Treatment-related morbidity was manageable, with no serious acute reactions being reported. However, serious chronic complications, such as radiation enteritis, neuropathy, and pneumonitis were encountered. This is in keeping with the large size and/or deep-seated location of disease radiated in these patients, which required high prescription doses and treatment of radiosensitive tissues, such as lung, peripheral nerve, and abdominal viscera. Consistent with experience published from other centers (22, 23), we found late morbidity to be associated with high neutron doses and large treatment ports (Table 2). Table 3 summarizes the serious late complication rates (as defined by grade ≥ 3 RTOG scale toxicity) reported in the literature—these have ranged from 7% to 59%. Given the lack of other effective local treatments for patients with unresectable disease, it is reasonable to presume that neutron radiation may prevent many cases of severe morbidity by halting local disease progression.

CONCLUSION

Fast neutron radiotherapy is a potentially effective local treatment for nonosseous sarcomas. Neutron radiation is able to overcome high-risk features predictive for poor local control, including contaminated surgical margins, presence of gross disease, large initial tumor size, and chondrosarcoma histology. Results in the palliative setting are particularly encouraging; neutrons provide frequent symptomatic relief for gross disease with minimal serious chronic sequelae. Further prospective evaluation of this modality is warranted.

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