



RESPONSE OF SARCOMAS OF BONE AND OF SOFT TISSUE  
TO NEUTRON BEAM THERAPY

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Response of Sarcomas of Bone and of Soft Tissue  
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ABSTRACT

A total of 51 patients were treated at Fermilab for sarcoma of bone (25 patients) and soft tissue (26 patients). Neutrons were delivered in twice weekly fractions over 6-7 weeks to total doses between 20 and 26 Gy. Long-term local control (greater than 2 years) was achieved in 24 patients (47%). Overall local control rates were 44% in the bone sarcomas and 50% in the soft tissue tumors. Chondrosarcoma appeared relatively more responsive with 9 out of 16 (56%) controlled, compared to osteogenic sarcomas with 2 out of 9 (22%) controlled. Among the soft tissue tumors, liposarcoma (5/7 controlled) and neurogenic sarcoma (3/5 controlled) appear to be more responsive than other tumors. The overall survival rate was 40% in the entire series.

These results are comparable with international experience in neutron therapy of sarcomas of bone and soft tissues. Out of 323 soft tissue sarcomas treated with neutrons only to full dosage throughout the world, 201 (62%) were locally controlled. Similarly out of 74 sarcomas of bone so treated, 44 (60%) were controlled.

KEY WORDS: Neutron therapy, radioresistance, sarcoma, bone tumors, soft tissue tumors.

INTRODUCTION

Sarcomas of bone (osteosarcoma, chondrosarcoma) have traditionally been treated by either radical or conservative surgery, with or without systemic chemotherapy. When total tumor ablation can be achieved, both these methods yield a high rate of local control; the major cause of failure being distant metastases. When adequate surgery is not feasible due to the location of the tumor (in the axial skeleton, for example), or when surgery is refused for cosmetic or other reasons, irradiation has been used with curative intent.

Local control can be achieved with conventional (low -LET) radiation, but very high doses are required (between 70 and 90 Gy<sup>2,6,13</sup> for ablation of osteo or chondrosarcomas). Recommended doses are not well tolerated by the normal tissues, particularly since the treated fields are necessarily large, and the consequences of such treatments are often destructive. Limbs have been saved by intensive local radiotherapy for bone sarcomas; however, in a significant proportion of cases the deformity resulting from radiation fibrosis and contracture has necessitated amputation even in the absence of residual tumor. In the axial skeleton, where the target volume may impinge upon vital organs, it may be difficult if not impossible to deliver adequate doses for these tumors. For these reasons sarcomas of bone have

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generally been classified as "radioresistant", and radiation has been considered only when surgery is contraindicated.

Sarcomas of soft tissue, of which the commonly encountered histological types include fibrosarcomas, liposarcomas, and tumors of muscle and nerve-sheath origin, are in general also relatively radioresistant, at least to conventional low-LET radiation. The accepted treatment for these malignant connective tissue tumors is surgical resection with a more or less generous margin followed by postoperative irradiation to the operative site and surrounding tissues for ablation of residual microscopic disease. This approach has proved highly effective in achieving local control in the majority of sarcomas in this category.<sup>3,11</sup> However, surgery may not be feasible when these tumors occur in the region of the neck or trunk, and may be undesirable when a nerve-sheath is involved and resection would consequently produce a paralyzed limb. In these non-resectable soft tissue sarcomas conventional radiation has been tried to maximally tolerated doses, but is curative only in a small proportion of patients so treated.<sup>1,7,12</sup> The majority of sarcomas of soft tissue are therefore also classified as relatively "radioresistant".

A number of recent reports suggest that many histological tumor types classified as resistant to conventional radiation respond satisfactorily to high-LET radiations including neutron

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beams. Sarcomas of both bone and soft tissue are no exception. Neutron beam therapy facilities in Europe (EORTC,<sup>14</sup>), Japan (CHIBA<sup>8</sup>), Houston (TAMVEC<sup>10</sup>), Washington (MANTA<sup>9</sup>) and Fermilab (this report) consistently report long term local control rates in excess of 60% in non-resectable sarcomas of both bone and soft tissue (Table 1).

The object of this report is to present our experience with these tumors at Fermilab and to explore the possible future role of neutron beam therapy in their management.

MATERIALS AND METHODS

During the period of study, 1976 to 1981 inclusive, 25 patients were treated for bone sarcomas and 26 for sarcomas of soft tissues. The response was evaluated at the end of 1983, so the follow-up period ranged from two to six years. The histological subtypes and the corresponding local control rates are listed in Table 2 together with data on the size and location of the tumors when treatment commenced.

In addition, the target absorbed dose, minimum tumor dose, maximum or peak dose, number of fractions and overall treatment time were recorded for each patient. From these data, dose-effect relationships for sarcomas of both bone and soft tissue were

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evaluated in regard to survival, local control of the disease and the associated risk of complications. The observed local control and complication rates at various dose levels provide the information necessary to estimate the probability of uncomplicated control as a function of dose, from which the optimal neutron dose for treatment of these tumors can be determined.

### RESULTS

As shown in Table 2, the overall local control rates for sarcomas of bone and soft tissue are about the same, approximately equal to 50%. This is slightly lower than the average of data on these two tumor types reported from various centers (Table 1), which is approximately 60%. The difference can probably be accounted for by the exceptionally advanced tumors referred for treatment to the Fermilab Neutron Therapy Facility.

Significant complications rates were relatively high in this series, affecting 16 patients (36%) (Table 3). Severe complications, affected 9 patients and comprised severe fibrosis of muscle and subcutaneous fascia (2 patients), sciatic neuropathy with paresthesia and/or foot drop (2 patients), periarticular fibrosis with loss of joint mobility (1 patient), cartilage necrosis (? patients), and bowel injury (2 patients) One complication was fatal; no other side-effects were sufficiently

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serious to warrant surgical intervention. Although classified as "severe", in no case were these complications considered to be as distressing as the disability which would have ensued from surgical extirpation of the growth.

The probability of uncomplicated control, that is local ablation of the growth without significant complications, is estimated to be 28% for the whole series (Table 3). The dose effect analysis clearly shows that the optimal dose in this series is confined to a narrow range between 22 and 24 Gy, where the local control rate is 61% with 33% complications yielding a maximum probability of uncomplicated control of 41%. There is a correlation between the risk of complications and the target absorbed dose received, with the complication rate becoming unacceptably high with doses above 24 Gy. The probability of local control also appears to increase with increasing dosage, being approximately 25% in patients receiving less than 22 Gy, reaching 61% in the optimal range (22 to 24 Gy), and being difficult to determine in patient's treated with doses greater than 24 Gy (since only 4 out of 12 patients treated in this dosage range survived for sufficient follow-up).

Among the 24 patients with local control (Table 2), 11 have died with distant metastases during the follow-up period. This has the effect of reducing the crude survival rate for the entire

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series to 39% (40% for the bone sarcomas, 38% for the soft tissue tumors). The survival rate for soft tissue sarcomas is considerably lower than the local control rate (Table 2). It should be noted that in the case of chondrosarcomas, all patients with local control remain alive and well, whereas 3 out of 13 patients with locally controlled soft tissue sarcomas have died. The cause of death in these three patients was treatment complication (1 patient), bronchopneumonia (1 patient) and diabetes (1 patient).

### DISCUSSION

Prior to the era of high-LET radiation, the role of radiation therapy in the treatment of osteosarcoma was negligible. With orthovoltage Roentgen rays, it became clear that doses of radiation which could be tolerated by the overlying skin had little influence on this tumor, which was consequently classified as radioresistant. With megavoltage radiations, higher doses were delivered and some measure of control was achieved with doses of 70 Gy or higher. Tudway<sup>13</sup> (1961) achieved local control in 5 out of 9 patients treated with doses of 60 to 80 Gy delivered between 40 and 90 days. More recently, Beck, et al.,<sup>2</sup> (1976) treated 21 patients with 75 ( $\pm$ 5) Gy in daily fractions over 55 to 65 days. In none of these patients was local control achieved. A larger series (43 patients without overt metastases out of a total of 72

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referred) were treated by De Moor<sup>6</sup> (1975) with doses of 72 ( $\pm$ 5) Gy in daily fractions over 40 to 50 days (2.2 Gy per day), and of 27 patients in the series followed for 5 years 9 have remained alive and well, 18 dying of metastases. In this series 11 amputations were carried out 6 months or more after radiation and in 6 of these no viable tumor was found. Survival was thus 21% of all patients treated radically or 12.5% of the whole series, and local control was achieved in approximately 1/3 of patients so treated.

The foregoing examples are typical of radiotherapeutic experience in megavoltage radiation of osteogenic sarcoma. By contrast in the Fermilab series (followed for 2 or more years) 11 out of 25 patients treated with neutrons are alive and well. Essentially similar results have been reported from other centers<sup>9,12,14</sup> making a total of 44 long term controls out of 74 patients treated (control rate 60% Table 1). None of the patients treated at Fermilab and few if any of those treated elsewhere, have required amputation because of radiation injury. This is in contrast to experience with megavoltage photons where approximately 2/3 of patients with controlled disease have required amputation because of the functional damage to the limb by the radiation.

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Although this was not a randomized study, and indeed randomization is hardly acceptable in the light of the dismal results observed with photon irradiation, it would appear that both local control and overall survival are markedly better with neutrons. The consistent results in four widely separated neutron therapy facilities, differing in patient population, beam quality and treatment philosophy, suggest that the observed results are not fortuitous but do represent a significant advantage associated with the high-LET radiation.

Results with soft tissue sarcomas appear to be similar to those observed with bone sarcomas, 13 out of 26 patients at Fermilab being controlled, 10 of whom are alive and well. This is consistent with the international experience now totaling 203 local controls out of 328 patients treated (control rate 62%). However, in this instance the question of the comparative efficacy of megavoltage photons remains to be evaluated, particularly in view to the wide range of histological types, with widely varying tendencies to recur and disseminate, encountered in this series.

It is generally believed that the radioresistance of soft tissue sarcomas is associated with the large capacity of the tumor cells to accumulate and repair radiation damage. Existence of a significant hypoxic fraction within the tumor cell population would further enhance this resistance to conventional

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radiotherapy. For these reasons a trial of high-LET radiations seemed appropriate and several other centers have initiated trials on neutron beam therapy in these tumors. The largest series so far reported was from EORTC (Europe) where a high local control rate (108 out of 189 patients treated) was reported.

In this country, Salinas et al.,<sup>2</sup> reported 29 extensive soft tissue sarcomas treated with a variety of fractionation schedules: (1) Neutrons only, twice weekly, (2) Neutrons only, four times weekly, (3) Neutron boost following photon irradiation, and (4) Mixed beam irradiation 2 neutron fractions and 3 photon fractions per week. Sixty-nine percent (20/29) of patients had local control of their tumor. No distinct superiority of any one fractionation schedule over another could be demonstrated. However, local control was better for patients who received doses greater than 21 Gy.

Catterall<sup>4</sup> reports achieving local control in 23 out of 28 patients (82%) treated at the Hammersmith neutron facility [d(15)Be reaction] to a dose of 15.6 Gy in 12 fractions over four weeks. However, 9 out of 28 (32%) developed major complications, probably due to the poor depth dose characteristics of the neutron beam. In Japan, Morita et al.,<sup>8</sup> have treated 12 patients with soft tissue sarcomas using the neutron beam at the NIRS facility [d(30)Be] and achieved a local control rate of 58% (7 out of 12).

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Local control rates observed in 8 different neutron therapy centers appear to be consistent (Table 1), varying from 50% at Fermilab to 80% or more in other centers depending upon tumor type and volume. The data in Table 2 suggest that liposarcomas and neurogenic sarcomas (Schwannomas) are more responsive than tumors of muscle or connective tissue. The optimal dose in our series appears to be between 22 and 23 Gy (Table 3), essentially similar to that for bone sarcomas.

It is concluded that, neutron beam irradiation is an effective option in the management of non-resectable bone sarcomas, particularly chondrosarcomas. With soft tissue sarcomas the most effective treatment is surgery with elective post-operative irradiation, but neutron beam therapy is a viable alternative in the management of non-resectable tumors.

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Table 1Long-Term Control by Neutrons in Non-Resectable  
Sarcoma of Bone and Soft Tissue

<u>TUMOR TYPE</u>	<u>FACILITY</u>	<u>TREATED</u>	<u>CONTROLLED</u>	
SARCOMA OF BONE	MANTA (9)	7	6	
	CHIBA [Japan] (12)	18	15	
	Essen (14)	24	12	
	Fermilab*	25	11	
	<b>TOTAL</b>	<b>74</b>	<b>44</b>	<b>(60%)</b>
SOFT TISSUE SARCOMA	Houston (10)	29	20	
	Hammersmith (5)	28	23	
	Amsterdam (1)	13	8	
	Hamburg-Eppendorf(7)	24	20	
	MANTA (9)	7	4	
	CHIBA (12)	12	7	
	EORTC [Europe] (14)	189	108	
	Fermilab*	26	13	
<b>TOTAL</b>	<b>328</b>	<b>203</b>	<b>(62%)</b>	

\*This report.

Table 2

Sarcoma of Bone and Soft-Tissue (Fermilab 1976-1981)

PATHOLOGY	NUMBER	SIZE		SITE			RESULT	
		<5 cm	>5 cm	Head	Trunk	Limb	ALIVE (%)	CONTROL (%)
<u>BONE:</u>								
Osteosarcoma	9	3	6	4	4	1	1 (11%)	2 (22%)
Chondrosarcoma	16	9	7	6	9	1	9 (56%)	9 (56%)
TOTAL	25	12	13	10	13	2	10 (40%)	11 (44%)
<u>SOFT-TISSUE:</u>								
Liposarcoma	7	2	5	1	4	2	4 (57%)	5 (71%)
Fibrosarcoma	8	4	4	1	5	2	1 (13%)	3 (38%)
Leiomyosarcoma	5	3	2	1	4	0	0 (0%)	1 (20%)
Schwannoma	3	0	3	0	1	2	3 (100%)	3 (100)
Synovioma	3	2	1	0	1	2	0 (0%)	1 (33%)
TOTAL	26	12	14	3	15	8	10 (38%)	13 (50%)
ALL SARCOMAS:	51	24	27	13	28	10	20 (39%)	24 (47%)

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Table 3

SARCOMA (1976-1981): Response to Neutron Irradiation

DOSE RANGE (Gy)	BONE			SOFT TISSUE			TOTAL			RATES		
	Nr.	Alive	Contr.	Nr.	Alive	Contr.	Nr.	Controlled	Complications	Cure %	Compl.	% PUC*
18-20	1	0	0	4	2	1	5	1	1	25%	25%	19%
20-22	3	2	1	4	1	1	7	2	2			
22-24	12	8	8	6	2	3	18	11	6	61%	33%	41%
24-26	4	0	0	6	3	3	10	3	4	(36%)	50%	18%
26-28	1	0	0	3	1	2	4	2	3			
TOTAL	21	10	9	23	9	10	44	19	16	43%	36%	28%
PERCENT	-	48%	43%	-	39%	43%	-	-	-	(+8%)	(+8%)	-

\*PUC = Percent Uncomplicated Control (maximal at 23 Gy when PUC = 41%).