

**LIGHT ION IRRADIATION FOR
UNFAVORABLE SOFT TISSUE SARCOMA**

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Abstract: Between 1978 and 1989, 32 patients with unfavorable soft tissue sarcoma underwent light ion (helium, neon) irradiation with curative intent at Lawrence Berkeley Laboratory. The tumors were located in the trunk in 22 patients and head and neck in 10. Macroscopic tumor was present in 22 at the time of irradiation. Two patients had tumors apparently induced by previous therapeutic irradiation. Follow-up times for surviving patients ranged from 4 to 121 months (median 27 months). The overall 3-year actuarial local control rate was 62%; the corresponding survival rate was 50%. The 3-year actuarial control rate for patients irradiated with macroscopic tumors was 48%, while none of the patients with microscopic disease developed local recurrence (100%). The corresponding 3-year actuarial survival rates were 40% (macroscopic) and 78% (microscopic). Patients with retroperitoneal sarcoma did notably well; the local control rate and survival rate were 64% and 62%, respectively. Complications were acceptable; there were no radiation related deaths, while two patients (6%) required operations to correct significant radiation-related injuries. These results appear promising compared to those achieved by low-LET irradiation, and suggest that this technique merits further investigation.

Key Words: Particles, Light Ions, Radiotherapy, Retroperitoneum, Head and neck, Sarcoma

Introduction

The combination of conservative surgery and radiotherapy (with or without chemotherapy) has become widely accepted as the standard treatment for soft tissue sarcomas arising in the extremities. Local control rates of 80-97% and long-term survival rates of 60-80% have been achieved using this approach [6,14,15,17,20,23,24]. These results appear equivalent to those achieved with radical, non-limb sparing surgery such as amputation. Total radiation doses on the order of 6000-6600 cGy appear sufficient to eradicate residual microscopic sarcoma [6,14,20,23], while macroscopic sarcomas require substantially higher doses (6500-8000 cGy) to achieve even modest local control rates [6,14,26]. Fortunately, many extremity lesions can be grossly resected, and the normal tissues of the limbs are able to tolerate post surgical radiation without unacceptable sequelae.

Patients with soft tissue sarcoma arising in non-extremity sites constitute an unfavorable subgroup. Approximately 40% of primary soft tissue sarcoma arises in the trunk or head and neck [6,23,14]. In these locations, complete resection of tumor is usually impossible [6,7,10,14], and the adjacent normal tissues may be unable to tolerate sufficient radiation to control residual disease. Not surprisingly, the outcome for patients with such tumors is substantially worse. Local failure rates for retroperitoneal sarcoma lie in the 46-77% range, with long-term survival rates of only 16-54% [6,6,12,17,21,25]. The results with head and neck sarcoma have been equally poor with long term survival rates of 32% and local failure rates on the order of 50% [6,9,14,21].

Several new treatment approaches (including combined surgery, irradiation and chemotherapy, intraoperative irradiation, neutron irradiation, and light ion irradiation) have been explored in an attempt to improve the outcome of non-extremity soft tissue sarcomas. Light ion irradiation is attractive because these charged particle beams possess both radiobiological and physical dose-distribution advantages over megavoltage X-ray beams.

From a physical standpoint, particle beams have sharp distal and lateral beam edges and a variable depth of penetration, allowing precise delivery of high radiation doses to the tumor while avoiding irradiation of adjacent normal tissues [11]. These properties can be particularly advantageous when irradiating tumors in head and neck or truncal locations where normal tissues such as spinal cord have limited radiation tolerance [5,22]. Light ion beams also have high LET qualities which produce biological behavior similar to neutrons. Compared to X-rays, there is: 1.) reduction in the oxygen enhancement ratio (OER) with proportionately greater killing of hypoxic cells, 2.) less variation in cell-cycle related radiosensitivity, and 3.) less capability for repair of radiation injury especially potentially lethal damage (PLDR). This last property may be of maximum importance in treating sarcoma with slow growth parameters which can repair damage from low LET Xrays but are unable to do so when treated with high LET charged particles [2,11].

These qualities result in increased relative biological effectiveness (RBE) at depth compared to low-LET megavoltage photon beams. Overall, the use of light ions allows delivery of higher, biologically more effective radiation doses with sparing of adjacent normal tissues.

This retrospective review reports the phase I-II Lawrence Berkeley Laboratory experience over the past decade using light ions in the treatment of unfavorably located soft tissue sarcoma.

Materials and Methods

Patient characteristics. Between 1978 and 1989, 32 patients with truncal or head and neck soft tissue sarcoma underwent light ion irradiation with curative intent at Lawrence Berkeley Laboratory (LBL). All patients were treated on clinical protocols approved by the University of California Human Use Committee and gave informed consent to the irradiation procedure.

Two patients had sarcomata which were believed to have been induced by prior therapeutic irradiation. Six other patients had recurrent tumors which had failed previous treatment. Macroscopic residual tumor was present in 22 patients at the time radiation was started, while 10 patients were treated for microscopic tumor. Of the 10 patients with microscopic residual, 8 had grade 2 or 3 tumors, and two had grade 1 tumors (one of which was recurrent, the other arising in a paranasal sinus with perineural invasion). Of the 22 patients with gross residual tumor, only three had grade 1 sarcoma, eight had grade 2 sarcoma, 10 had grade 3, and grade could not be determined in 1 patient. (Gross residual tumor was present in the patient with indeterminate grade.)

The histologic types included 10 malignant fibrous histiocytoma, 6 neurofibrosarcoma, 6 liposarcoma, 3 leiomyosarcoma, 3 undifferentiated sarcoma, 1 clear cell sarcoma, 1 recurrent rhabdomyosarcoma, 1 mesenchymal sarcoma, and 1 fibrosarcoma (Table I). Fourteen tumors arose in the retroperitoneum, 10 in head and neck locations, 3 in the thorax, 4 in the pelvis, and 1 in the liver. 18 patients were men and 14 were women (Table II).

Treatment technique. Following maximal resection of tumor, patients underwent treatment planning and irradiation with either helium or neon ions. Thirteen patients received chemotherapy either before, during, or after irradiation; however, there was no uniformity for either the agents used (Vincristine, Cytosin, Adriamycin, cis-Platinum, and DTIC in various combinations) or the routes of administration (IV and intra-arterial). The light ion radiation therapy technique has been described previously [3,4,5,22]. 18 patients received X-ray therapy as part of their irradiation. Both helium and neon charged particle beams were used at LBL depending on beam availability and tumor location but neon was preferred because of its high LET properties. Radiation doses given were expressed in terms of "equivalent dose" (cGyE), i.e., equivalent to the dose of conventionally fractionated megavoltage X-rays which would produce the same acute biologic effect as the particle beam. The equivalent dose for light ions was calculated using the formula:

$$\text{physical cGy} \times \text{RBE} = \text{equivalent cGyE}$$

[13,18]. The neon RBE for acute radiation reactions relative to

megavoltage X-rays is 2.0-3.5 (average 2.5), depending on fraction size, type of tissue irradiated, beam energy, size of the extended Bragg peak, and biological endpoint chosen [2,19,27]. The corresponding RBE for the helium beam is 1.2-1.4 (average 1.3); for CNS the helium RBE is about 1.6 and neon RBE about 4.0 [4,8,16,19]. The RBE for megavoltage X-rays is 1.0 by definition. The total equivalent dose delivered was calculated using the following equation:

$$\text{cGyE}_{\text{neon}} + \text{cGyE}_{\text{helium}} + \text{cGy}_{\text{xray}} = \text{total equivalent dose (cGyE)}.$$

Radiation Dose. The intent of the treatment was to deliver a minimum tumor dose of 6000 cGyE for microscopic residual and 6600 cGyE for gross residual tumor. This was not achieved in 5 patients: 2 clinically deteriorated during treatment and had their radiation stopped after total doses of 2800 and 3750 cGyE. Another patient had a radiation-induced sarcoma and received only 5100 cGyE (cumulative dose in treatment field 9500 cGyE). Two other patients with paranasal sinus sarcomas received only 5600 and 5950 cGyE because of tumor proximity to brain and the excessive risk of CNS injury with higher doses. All 5 of these patients were included in the survival and local control analyses. The remaining 27 patients received total doses ranging between 6000 -8230 cGyE (median 6600 cGyE).

Data Analysis and Statistical Methods. No patient was lost to follow-up. Patients were analyzed with respect to local control and

survival, starting from the date irradiation began. There were no deaths due to intercurrent illness. Actuarial 3-year local control and survival rates were calculated using the method of Berkson and Gage [1]. Follow-up times for surviving patients ranged from 4-121 months, with a median of 27 months. Because of the heterogeneity of the patients, meaningful risk factor and dose-response analyses could not be performed.

Results

All patients. Ten of the 32 patients eventually recurred within the particle radiation field, and 13 developed distant metastases. The overall 3-year actuarial local control rate was 62%. Twelve of the 32 patients have died. The 3-year actuarial survival rate for the entire group was 50%. Only 3 patients died from uncontrolled local tumor alone; 4 died as a result of distant metastases with local control, and 5 died with both local failure and distant metastases. At the time of this analysis, 5 patients were alive with disease (1 with local failure alone, 3 with distant metastases, and 1 with both distant metastases and local failure).

Temporal pattern of failure. The time course for local failure was relatively rapid; 90% (9/10) of local failures took place within 2 years of treatment, and the last occurred at 31 months. The survival pattern was similar; two-thirds (8 /12) of deaths occurred during the first year of follow-up, and all others within 3 years of treatment.

Macroscopic disease. Twenty-two patients were irradiated with macroscopic residual tumor, and 10 failed locally. Two of these failures occurred in patients with incomplete treatment; 2 others had low doses because of radiation induced tumor and tumor proximity to brain respectively. Thus only 6 of 18 patients with gross disease failed after adequate radiation doses. For all patients with macroscopic disease, the 3-year actuarial local control rate was 48%. 11 patients in this group died; the 3-year actuarial survival rate was 40%.

Microscopic disease. None of the 10 patients treated for residual microscopic tumor failed locally (local control 100%). Only one patient in this group died; the 3-year actuarial survival rate was 78%.

Head and neck sarcoma. Three of the 10 patients irradiated for head and neck sarcoma failed locally. The 3-year actuarial local control rate was 65% for this site. Three died; the 3-year actuarial survival rate was 57%.

Truncal sarcoma. This group included 22 patients with tumors arising in the retroperitoneum, mediastinum, pelvis, and viscera (liver). Seven failed locally, with a 3-year actuarial local control rate of 62%. The 3-year actuarial survival rate was 55%.

Retroperitoneal sarcoma. Fourteen patients from the trunk group had retroperitoneal sarcoma; the 3-year actuarial local control rate for these patients was 64% with a 3-year actuarial survival rate of 62%.

Radiation-induced and recurrent sarcoma. Both of the patients with radiation-induced sarcoma eventually died from disease. Of the 6 who were treated for recurrent disease, only 2 remain with no evidence of disease at present.

Complications. Despite the high doses of radiation and difficult tumor location, complications were relatively infrequent. No patient died from radiation-related injury. One patient with a pelvic malignant fibrous histiocytoma developed sciatic neuropathy secondary to radiation fibrosis, but has not required hospitalization for this problem. Two patients with retroperitoneal sarcomas who received a large volume of the abdomen treated with megavoltage Xray prior to the light ion therapy boost developed severe radiation stricture and required laparotomy; both are presently free of disease 50 and 55 months after treatment. One other patient required a minor operation: irradiation of an orbital liposarcoma caused orbital fibrosis and corrective surgery for strabismus was necessary. Although the same patient continues to have a dry eye, there has been no evidence of radiation retinitis and vision remains 20/20 in the irradiated eye.

Discussion

The results from this phase I-II study establish that light ion irradiation of unfavorable head and neck or truncal sarcoma is clinically feasible and can be accomplished with an acceptably low complication rate. The 3-year local control and survival rates reported here appear sufficient to evaluate long term outcome, as there have been no local recurrences or deaths developing later than 3 years after particle irradiation. This pattern of early treatment failure also matches the experience of soft tissue sarcoma treated with conventional megavoltage irradiation [6].

The experience with conventional treatment of retroperitoneal sarcoma is illustrative of the difficulties encountered with non-

extremity sarcoma. Although the current light ion series consists of a small number of selected patients, the results appear encouraging, and suggest that this technique might offer an improvement over conventional irradiation (Table III). Cody et. al. reported on 158 retroperitoneal sarcoma patients treated at Memorial Sloan-Kettering between 1951-1977; their 5-year survival rate after complete excision was 40%, and after incomplete resection only 3% [7]. The local recurrence rate following complete resection was 77%. Not all of the patients in that series received adjuvant irradiation or chemotherapy. The NCI experience in 36 patients with completely resected retroperitoneal sarcoma was similar; the 3-year actuarial survival rate in that series was 50%, with a 47% local recurrence rate [21]. Those patients were treated aggressively with multiple modalities; all were irradiated and many received adjuvant chemotherapy. The Massachusetts General Hospital series of 17 irradiated patients (most of whom also received chemotherapy) achieved actuarial 5-year survival and local control rates of 54% [26].

More recently, 15 retroperitoneal sarcoma patients undergoing intraoperative (20 Gy) plus external beam irradiation (35-40 Gy) were compared to 20 patients treated with external beam irradiation alone (50-55 Gy) in a randomized, prospective trial [12]. All the patients in that study underwent complete resection, and many also received adjuvant chemotherapy. 5-year actuarial survival rates were approximately 40% for both arms, and were not significantly different. The 3-year local control rate in the IORT arm was approximately 70%, compared to roughly 55% in the control arm, not a statistically significant difference. The current LBL results in retroperitoneal tumors (14 patients, 10 of whom had incomplete resections) appear promising with a 3-year actuarial

survival rate of 62% and corresponding local control rate of 64%.

We plan to treat a larger, prospective series of patients with light ion radiation therapy to evaluate the relative value of dose distribution as exemplified in helium ions versus the greater biological advantages of high LET ions such as neon. Of particular interest will be treating those patients with either unresectable or partially resectable (large residual) tumors. Potentially predictive assays to assist in selecting patients whose tumors might be preferentially better treated with high LET beams will be studied in our laboratory.

Summary

Light ion irradiation allows higher doses to residual tumors in the retroperitoneum and other critical locations through its superior dose localization properties. There may also be a distinct advantage for slow growing sarcoma where the potential lethal repair of irradiation is diminished by the use of high LET beams. As this may not be a selective process, the advantageous dose distributions of light ions are clearly indicated to diminish normal tissue effects.

Addendum: Since the analysis of this data, one additional patient with microscopic residual disease in the retroperitoneum has had a marginal recurrence at 34 months post therapy. This occurred at the distal deep margin of the treatment volume and represents an error in target volume delineation, rather than a resistant tumor. The lesion has been resected in a second operation.

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Table I

HISTOLOGY OF SOFT TISSUE SARCOMA
TREATED AT LBL

Malignant Fibrous Histiocytoma	10
Neurofibrosarcoma	6
Liposarcoma	6
Leiomyosarcoma	3
Undifferentiated Sarcoma	3
Others	4

Table II

ANATOMIC LOCATION

Retroperitoneum	14
Head/Neck	10
Thorax	3
Pelvis	4
Liver (Abd)	1

SEX: Male	18
Female	14

Macroscopic Residual:	22
Microscopic Residual:	10

Table III

<u>Series (Ref)</u>	<u># Pts.</u>	<u>5-year Survival</u>	<u>Local Control</u>
MSKCC (Cody)	158	CR: 40% IR: 3%	23% NS
NCI (Potter)	36	50%	50%
MGH (Tepper 1)	17	54%	54%
NCI (Kinsella 1) (IORT)	15	40%	70%
(XRT)	20	40%	55%
LBL (current series)	14	62%	64%

Treatment results in **retroperitoneal sarcoma** from various institutions. Because of wide variations in radiation technique, use of chemotherapy, and the amount of residual tumor at the time of irradiation, comparisons are difficult. See text for details. (CR = completely resected; IR = incompletely resected)

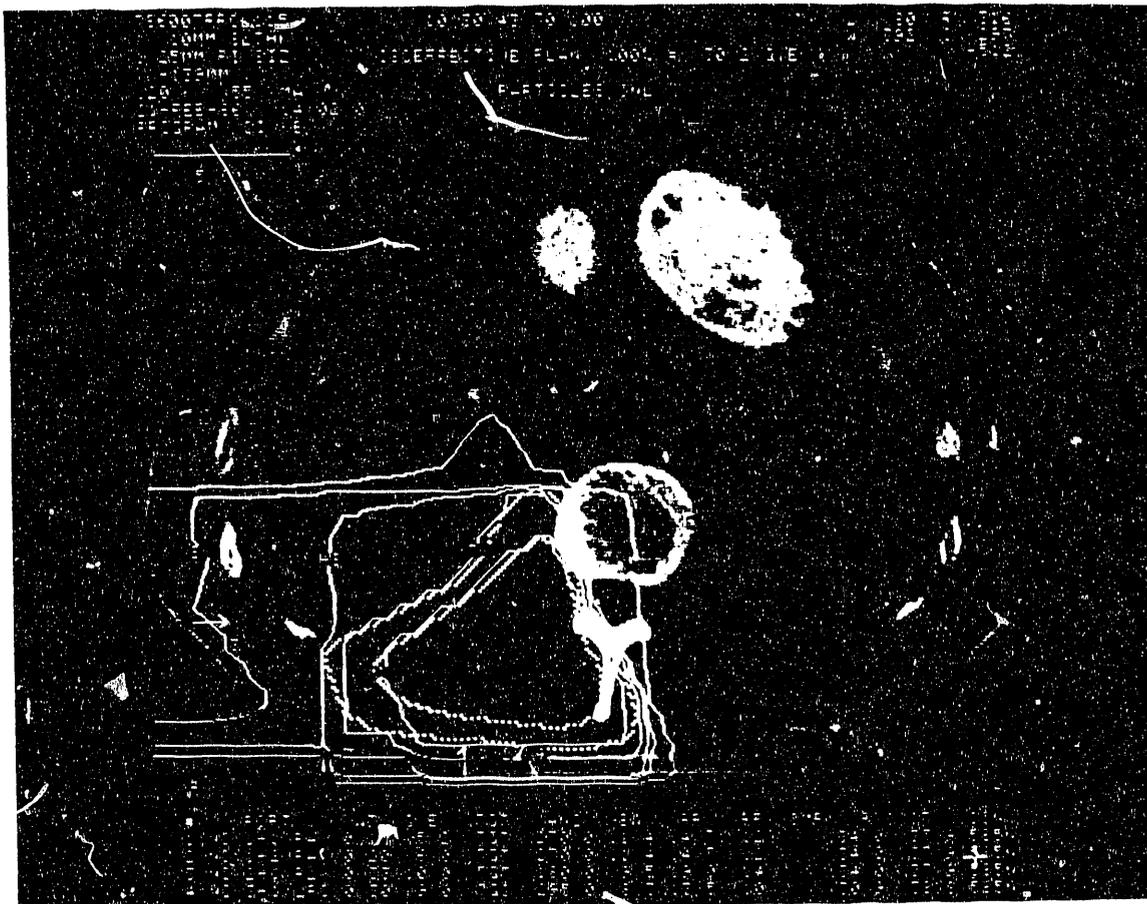


Figure 1. Isodose plan for neon ion irradiation of 49 y.o. w/m with recurrent malignant fibrous histiocytoma of right retroperitoneal area, post debulking resection. Pt received 4000 cGy xray therapy followed by a reduced volume boost with neon ions of 3000 cGy equivalent. He remains free of disease more than 4 years post therapy.

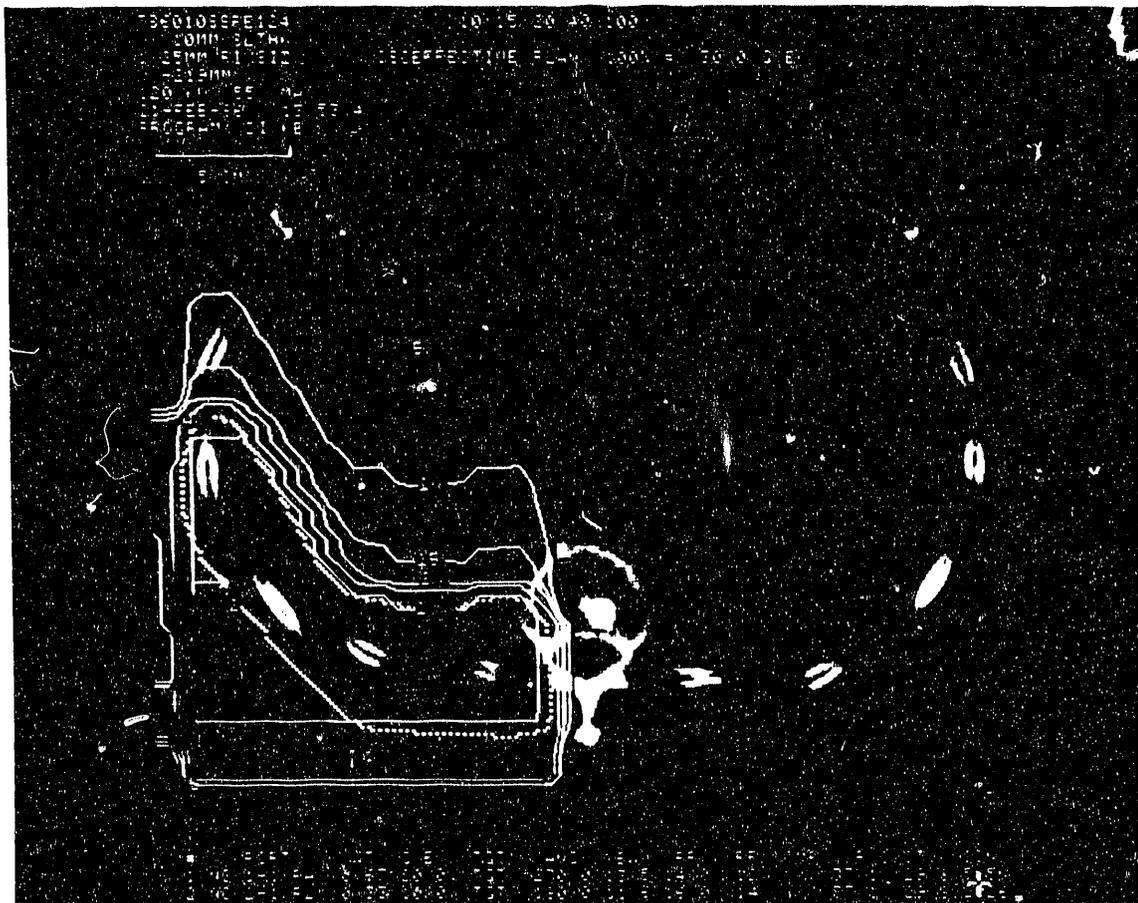


Figure 2. Isodose plan for same patient at a different level. The physical parameters of the neon ions permitted sparing of the spinal cord from receiving more than about 20% of the dose.

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