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The Role of Radiotherapy in the Treatment of Bone and Soft-tissue Sarcomas

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INTRODUCTION

The role of radiation therapy in the management of soft-tissue and bone sarcoma has changed over the past 40 years and it continues to evolve. Radiotherapy is currently accepted as a standard adjuvant for most soft-tissue sarcomas of high grade, while the routine use of adjuvant radiotherapy for low-grade sarcomas is controversial. Preoperative chemotherapy has largely replaced radiotherapy in the local management of osteosarcoma.

There are several reasons for the initial belief that sarcomas were radioresistant. Until the 1960s megavoltage radiation beams were not generally available, and successful treatment of bulky, often deep-seated sarcoma was limited by the poor depth of penetration of lower-energy orthovoltage beams.[1,2] Historically, single-modality treatment (surgery or radiation) was often employed to treat tumors which more frequently were allowed to reach large size prior to medical intervention. Finally, the previously held belief, that the rate of clinical regression was a measure of radiocurability, is no longer considered valid.

It is now recognized that tumors are often composed of dense stroma containing blood vessels, connective tissue, and mucinous or osteoid matrix, and that these elements may resolve slowly after sterilization of malignant cells. With the observation that radiotherapy is most successful in eradicating microscopic extensions of tumor, the routine application of adjuvant radiation has made possible reductions in the volume of resected "normal tissue", and has allowed limb-sparing procedures to be utilized without significant reductions in local control or disease-free survival.[3,4] Contemporary issues which remain unresolved pertain to the timing and volume of adjuvant radiotherapy for soft-tissue and Ewing's sarcoma, and to the identification of more effective systematic therapy for soft-tissue and bone sarcoma.

RADIOBIOLOGY

Contrary to previous beliefs, clonagenic survival assays of human soft-tissue sarcoma and bone sarcoma cell lines reveal no consistent evidence of intrinsic resistance to radiation. The surviving fraction at 2 Gray (SF2 General Electric) has been accepted as a clinically relevant measure of radiation sensitivity. Ruka *et al.*,[5] Mundt *et al.*,[6] and Dahlberg[7] evaluated SF2 Gy values in carcinoma, sarcoma, and normal fibroblast cell lines. The average SF2 Gy value for sarcoma was 0.24 (summarized in Table 5.1). Although the tumor cells which had the highest SF2 Gy values in the Mundt analysis also developed local recurrence, SF2 values for sarcoma were lower than those for squamous carcinoma, and were not different from SF2 Gy values for normal fibroblasts.[5–7] In addition, the radiation dose required to locally control breast and squamous carcinoma following complete resection is identical to the dose required for local control of soft-tissue sarcoma. These observations suggest that the alleged "radioresistance" of sarcomas is without basis (see Figures 5.1 and 5.2).

RESULTS OF LOCAL TREATMENT OF SARCOMA

Soft-tissue Sarcoma

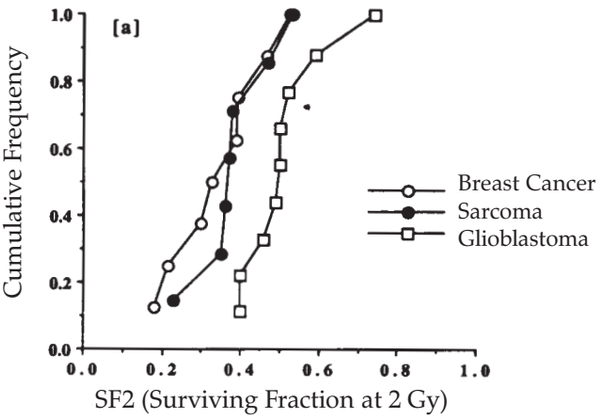
Surgery Alone

In highly selected patients, wide resection alone produces excellent local control rates (90% and higher, see Table 5.2). Criteria used to select patients for wide excision alone include: size less than 5 cm, superficial location, confinement within one fascial compartment, and resection margins ≥ 1–2 cm. Berlin and colleagues reported 137 patients treated with surgical resection without adjuvant radiation therapy to the primary site. Local control was achieved in 89% of resected patients with radical or wide margins, compared to only 34% of patients with "marginal" margins ($p = 0.05$). Multivariate analysis identified advanced age, open biopsy, and marginal resection as predictors of local recurrence.[8] In a later report from Sweden, by Rydholm *et al.*, limb-sparing surgery alone produced local control in 52 of 56 (92%) patients. In this report, sarcomas in the subcutaneous tissues were resected with a cuff of uninvolved fat and the layer of deep fascia below the tumor. Intramuscular tumors were treated with resection alone if there had not been an open biopsy, and if the undisturbed tumor could be removed via myectomy or limited (one muscle) compartmental resection. The principles of diagnostic evaluation and surgical resection described by Rydholm *et al.* in this report are informative and warrant review.[9]

Table 5.1 Radiobiologic parameters of soft-tissue sarcoma

Reference	*Sarcoma cell lines*	*Mean dosage (cGy)*	*Mean SF_2*
Ruka *et al.*[5]	7	120	0.39
Mundt *et al.*[6]	13	115.7	0.26
Dahlberg *et al.*[7]	12	90.1	0.124
Total	32	107	0.24

cGy = centigray; SF_2 = positron.



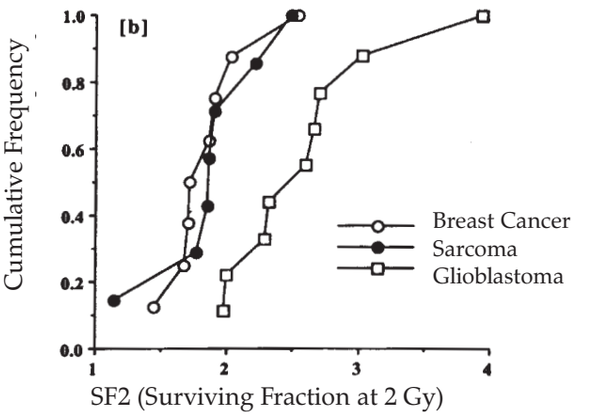


Figure 5.1 A comparison of radiosensitivity among sarcoma, breast cancer and glioblastoma cell lines as determined in Figure 5.2A by the surviving fraction at 2 Gy (SF_2), and in Figure 5.2B by the mean inactivation dose. These data demonstrate no difference in inherent radiosensitivity parameters between breast cancer and soft-tissue sarcoma cell lines as determined in the colony formation assay. Although the *in-vitro* parameters do not predict clinical responses, the doses used to successfully treat breast cancer are very similar to those used to locally control soft tissue sarcoma (from ref. 5).

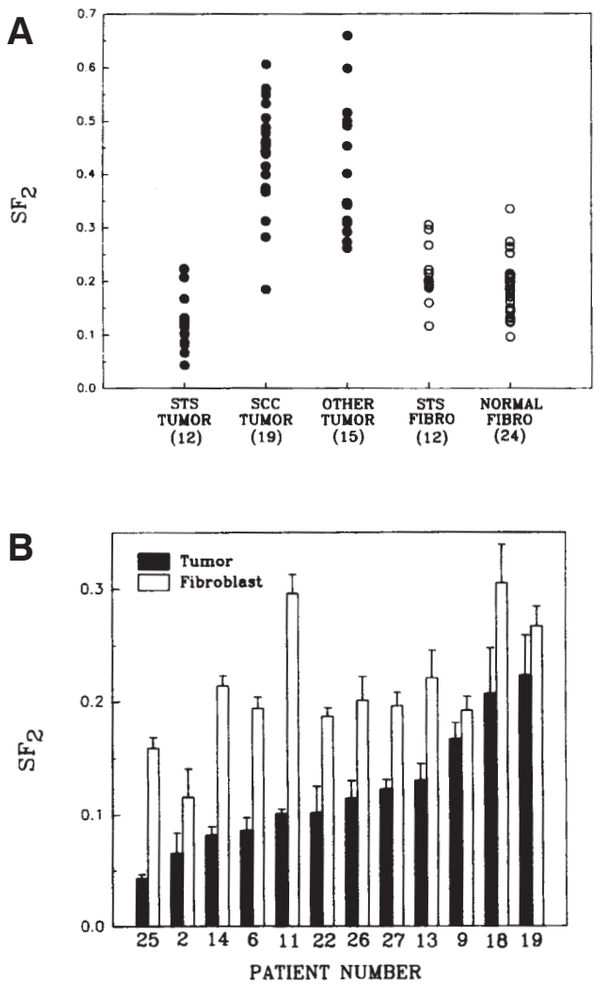


Figure 5.2 A comparison of the surviving fraction at 2 Gy (SF_2) values for soft-tissue sarcoma cell lines and several other cell types. In Figure 5.2A soft-tissue sarcoma (STS) tumor cell lines are compared to squamous cell carcinoma (SCC) cell lines, various other tumor cell lines, syngeneic fibroblast (STS Fibro) cell lines, and fibroblast cell lines from normal volunteers (Normal Fibro). These data demonstrate that there is no inherent radioresistance in STS cell lines. In Figure 5.2B a comparison is made of the radiosensitivity of STS cell lines and syngeneic normal fibroblast strains from the tumor-bearing host. Note the consistently more radiosensitive phenotype among tumor cell lines compared to normal fibroblasts from the same host. Patients number 11 and 27 represent lymphoma cell lines (from ref. 7).

Excellent local control following surgery alone in selected patients was also reported by Karakousis and co-workers. Of 152 patients reviewed, 143 (94%) had a limb-sparing procedure. Local control was achieved in 90% following surgery alone. For grade II and grade III tumors, local control was 88%.[10] Geer *et al*. reported

Table 5.2 Wide local excision alone for soft-tissue sarcoma

Reference	*No. of patients*	*Locally controlled*	*Percent*
Markhede (1982)	63	58	92
Berlin (1990)	76	66	87
Rhydholm (1991)	56	52	93
Geer (1992)	117	106	90.6
Karakousis (1995)	107	95	89
Gibb (1997)	35	35	100
Baldini (1999)	74	70	94.6
Total	528	482	91

excellent local control and survival for soft-tissue sarcoma < 5 cm in diameter following limb-sparing resection. The 5-year actuarial local disease-free survival following surgery alone was 92%. Multivariate analysis revealed only age > 50 years as a predictor of local recurrence.[11]

Most recently, Baldini *et al*. reported 74 patients with primary, nonmetastatic soft tissue sarcoma of the extremity or trunk who were treated with function sparing surgery and no radiation. Sixty patients had wide excision (1–2 cm margin of adjacent normal tissue), 13 patients had radical excision (entire muscle compartment), and one patient had a marginal excision. Sixty-eight (12%) had negative margins, five (7%) had microscopically positive margins and one patient had a grossly positive margin. Only four of the 74 patients developed local failure, for a local control rate of 95%. The actuarial rates for local control at 5 and 10 years are 96% and 93%, respectively. The only factor identified as a predictor of local recurrence was surgical margins less than 1 cm.[12] From these and other reports,[13,14] it is clear that selected subsets of patients can be treated with function-sparing resection alone. In the Swedish[9] and Brigham and Women's/Dana Farber[12] experiences, this constitutes approximately 30% of patients who present with soft-tissue sarcoma. Guidelines for the selection of patients for limb-sparing resection alone are listed in Table 5.3.

Radiation Alone

Analogous to observations regarding epithelial tumors > 5 cm in diameter, radiation alone is rarely adequate to produce durable local control of soft-tissue sarcoma. Normal tissue radiation tolerance often prohibits the radiation of bulky tumors to dose levels required for sterilization. Leibel *et al*. reported five patients with intermediate or high-grade tumors > 5 cm in diameter who were treated with radiation alone. None was locally controlled.[15] Tepper and Suit reviewed the

Table 5.3 Selection factors for considering surgery alone for sarcoma

	Yes	*Possibly*	*No*
Size	<5 cm	5–10 cm	>10 cm
Margins	>2 cm	1–2 cm	≤ 1 cm
Biopsy	FNA	Trucut	Open biopsy
Primary vs. recurrent	Primary	Recurrent, new site	Recurrent, old site
Fascial investment	Complete	Partial	Involved
Previous Surgery	No	Yes	Complete resection
Grade	I	II–III	—
Age	<50	—	>50

Massachusetts General Hospital experience with radiation alone for soft-tissue sarcoma. Patients were treated from 1971 to 1982 using megavoltage equipment to total doses of 64–66 Gy. Forty-four of 51 patients were evaluable with > 5 years follow-up. The 5-year local control rate was 33%. Local control for tumor ≤ 5 cm was 87%, for tumors 5–10 cm it was 53%, and for tumors >10 cm it was 30%. Total doses equivalent to <64 Gy were associated with poor local control.[16] Thus, conventional photon radiation alone will be unsuccessful in controlling the majority of soft-tissue sarcomas >5 cm. However, palliation of symptoms and the possibility of local control can be offered to patients who refuse resection, or who are surgically unfit. Distant metastases in patients with larger high-grade tumors pose the greatest limitations on survival. The results of radiotherapy alone for soft-tissue sarcoma from various series are summarized in Table 5.4.

The Role of Radiotherapy in Limb Salvage for Soft-Tissue Sarcoma

Early recognition that wide local excision (WLE) of the majority of high-grade sarcomas resulted in unacceptably high rates of local failure (20–70%),[17,18] led surgical oncologists of the 1950s and 1960s to advocate amputation as the procedure of choice.[18] With the development of megavoltage radiation beams in the 1960s, bulky, deep-seated tumors could be treated to high doses with relative sparing of skin and subcutaneous tissues. In the mid-1970s several institutions initiated clinical trials evaluating WLE combined with preoperative or postoperative radiation and chemotherapy. The goal of these studies was preservation of a useful, functioning limb.

Table 5.4 Radiation alone for soft-tissue sarcoma

References	*No. of patients*	*Local control*	*Year*
McNeer *et al.*[19]	25	14/25 (56%)	1968
Suit *et al.*[21]	18	15/18 (83%)	1975
Leibel *et al.*[15]	5	0%	1982
Tepper and Suit[16]	5 (<5 cm)	87%	1985
	17 (≥ 5–10 cm)	53%	
	10 (≥ 10 cm)	30%	

Retrospective analyses published in the late 1960s and early 1970s from Memorial Hospital in New York and MD Anderson Hospital suggested that acceptable local control rates could be achieved when a less than radical resection was combined with radiotherapy. McNeer *et al*. reported the Memorial Hospital experience from 1935 to 1959 in which 653 patients with soft-tissue sarcomas were treated with curative intent. Twenty-five were treated with radiation only, 46 received preoperative radiation, 96 received postoperative radiation and 486 received surgery only. A variety of radiotherapy techniques were used including orthovoltage, radium packs, cobalt 60, high-energy electrons and megavoltage photons. Total doses ranged from 1500 to 7000 rad; however, most patients received >3000 rad. From 1935 to 1945 radiation was routinely administered. From 1946 onward radical resection, including amputation, was emphasized. Patients with bulky tumors received preoperative radiotherapy to facilitate resection. During this period postoperative radiotherapy was given if it was felt that the margins of excision were close or positive. Radiotherapy alone was reserved for patients who refused surgery or who were medically inoperable. Local control was 75% following surgery alone, 56% following radiation alone, 63% following preoperative radiation, and 66% following postoperative radiotherapy. It was noted by the authors that patients with the less favorable prognoses received radiotherapy. The clinical response rate of 72%, and histologic complete sterilization rate of 33% produced by radiotherapy, prompted the authors to recommend routine preoperative radiotherapy in 1968.[19]

From 1961 to 1969, 57 patients with soft-tissue sarcomas who were recommended to receive amputation were treated by Suit and colleagues at MD Anderson Hospital with radiotherapy alone or combined with simple excision. Twenty-seven patients were treated with conventional fractionation and 30 patients were treated with high-dose radiotherapy and tourniquet-induced hypoxia. Local control was achieved in 87% (50/57). Thirteen patients (23%) required amputation.

Six patients treated with very high-dose radiotherapy (12,000–14,000 rad) and "tourniquet technique" required amputation for severe radiation toxicity. The remaining amputations were performed for persistent or recurrent disease (seven patients). Many patients were treated with grossly positive margins or with palpable tumor.[20] Several refinements in radiotherapy treatment technique emerged from these early experiences, such as avoidance of circumferential irradiation of limbs, the use of progressively smaller volumes of irradiation exposure (i.e. "shrinking-field" technique), and minimization of normal tissue exposure through complex field arrangements.[20,21] In an update of this series the results of 100 patients were reviewed. Local control was achieved in 87%. Seventy-five percent of patients retained a useful limb, and overall local control rates were similar to those achieved with amputation.[22]

Data from these and other institutions strongly suggested that alternatives to amputation, such as limited surgical resection and carefully planned radiotherapy, produced good local control rates and offered the possibility of preserving a functioning limb. Results from several early series are summarized in Table 5.5. While these studies disproved the myth of "radio resistance" which surrounded soft-tissue sarcomas, non-controlled retrospective series did not allow meaningful comparisons of radical surgery to limb-sparing surgery and radiotherapy. Prospective randomized trials were needed.

In May of 1975 the National Cancer Institute initiated a prospective randomized trial of radical surgery (amputation) and chemotherapy versus limited surgery, radiation and chemotherapy. Sixteen patients were randomized to receive amputation. There were no local recurrences in this group. Twenty-seven patients received limited surgery and postoperative radiation. There were four recurrences in the conservative surgery group (local recurrence rate = 15%). The difference in local recurrence rates was of borderline significance. There was no difference in disease-free or overall survival between these two groups (results are summarized in Table 5.6).[3]

In an update of their experience reported by Potter *et. al.* in 1986, local control following amputation and chemotherapy remained 100% (0/83 local failures), and local control following WLE and postoperative radiotherapy with or without chemotherapy was 92% (12/128) local failures. In this latter analysis of the randomized NCI studies of soft-tissue sarcoma the use of adjuvant chemotherapy was associated with improved local control in patients who were treated with limb-sparing surgery and radiotherapy.[23] The contribution of chemotherapy to local control has recently been described for head and neck, and truncal sarcomas treated in a European randomized trial,[24] and is also relevant when reviewing the most recent results reported from the NCI.[4]

Table 5.5 Surgery plus postoperative radiation for soft-tissue sarcomas – early results

Reference	*No. of patients*	*Local control*	*Year*
McNeer *et al.*[19]	94	62/94 (66%)	1968
Spittle *et al.*[271]	49	38/49 (80%)	1970
Suit *et al.*[20]	57	50/57 (87%)	1973

Table 5.6 Results of the NCI randomized trial of limb preservation: amputation versus resection and radiation[3]

Amputation	*Limb preservation*	P-*Value*
Sixteen patients	Twenty-seven patients	
Local control = 100%	Local control = 85%	0.06
Disease-free survival = 78%	Disease-free survival = 71%	0.75
Overall survival = 88%	Overall survival = 83%	0.99

After the seminal reports by McNeer, Suit, Lindberg, and Rosenberg and co-workers[3,19,20,21,25] which demonstrated that amputation could be avoided without significant reductions in local control or survival, postoperative radiotherapy was accepted as standard following WLE or limb salvage surgery for high-grade soft-tissue sarcomas. A number of reports from America and Europe have documented the success of WLE and postoperative radiotherapy. Local control in these reports ranged from 80% to 100%, and details are summarized in Table 5.7.[4,6,23,25–32]

Prognostic Factors for Local Control following Surgery and Postoperative Radiation

Although agreement exists that there is excellent local control following WLE and radiotherapy, a number of issues remain controversial regarding prognostic factors. Several of these prognostic factors are summarized in Table 5.8 and discussed briefly below.

Age

Age at diagnosis has been reported as a predictor of local control. Several multivariate analyses of prognostic factors which address local recurrence have been published by investigators at Memorial Sloan Kettering Cancer Center from 1988 to 1996.[11,33–35] In each of these, age >50 years (53 years in the report by Collin *et al.*[33])

Table 5.7 Results of limb preservation with excision and radiation for soft-tissue sarcoma

Reference	*No. of patients*	*Local control*
Yang *et al.*[4]	70	69/70 (98.6%)
Wilson *et al.*[27]	62	59/62 (95%)
Dinges *et al.*[28]	102	84/102 (82%)
Keus *et al.*[29]	117	99/117 (85%)
Fein *et al.*[30]	67	61/67 (91%)
Cakir *et al.*[41]	75	50/75 (67%)
Pao and Pilepich[47]	50	39/50 (78%)
Mundt *et al.*[6]	64	53/64 (83%)
Lindberg *et al.*[25]	300	233/300 (78%)
Total	907	727/907 (80%)

Table 5.8 Prognostic factors for local control following surgery and postoperative radiation

Factor	*Predictive value*	*Supported (references)*	*Not supported (references)*
Age	Controversial	8, 11, 33–38	23, 29, 39–45
Histology	Controversial	21, 25, 32, 34	4, 7, 23, 32, 40, 41
Grade	Controversial	10, 15, 20, 25, 28, 29, 33, 42, 47	23, 30, 34, 48
Location	Established*	20, 21, 25, 35, 38, 42, 51, 52	23, 28, 29, 32–34, 43, 44, 48, 53†
Depth	Controversial	29, 42	33, 34, 45, 47, 53, 54
Size	No predictive value	21	21, 23, 28–33, 35, 41, 43, 44, 53, 55
Margins	Established	29, 31–33, 37, 41, 43–45, 47, 48, 49, 53, 56, 58, 59, 62	4, 23, 24
Recurrent tumor	Established	28, 31, 33–35, 40,43, 44	29, 37
Radiotherapy target volume	Suggestive	6, 48	29
Radiation dose	Suggestive	28, 30	29, 41

*Tumor location is a significant predictor of local control when different major anatomic sites are compoared (i.e. extremity versus retroperitoneum).
†When different locations on an extremity are compared there is no predictive value.

was identified as an independent predictor of local recurrence and following conservative surgery and radiotherapy. The underlying biologic explanation for this finding is not discussed in these reports, which were recently reviewed.[36] Similar results were reported by Swedish investigators in 1982 and 1990.[8,14] In the earlier report, more advanced age was associated with local recurrence. However, when the model was corrected for the adequacy of surgical resection, age lost its prognostic significance.[14] Such a correction for interdependant variables was not discussed in the later report, despite the fact that patients diagnosed with malignant fibrous histiocytoma tended to be older than patients with other histologic types.[8]

Younger age was predictive of better local control in a multivariate analysis reported from the Princess Margaret Hospital. However, an explanation for this finding, and its implications for patient management were not offered.[37] More recently a report from the Danish Center for Bone and Soft Tissue Sarcomas described 316 patients with truncal and extremity sarcomas. Age >56 years was associated with increased local recurrence, and decreased survival. However, of the 316 patients reviewed, only 50 received adjuvant radiotherapy.[38] Age had no impact on local recurrence in multivariate analyses in nine other reports, including those from the NCI/NIH, MD Anderson, the French Federation, and Harvard Medical School.[23,29,39–45] It thus appears that, for local control following conservative surgery and radiotherapy, the significance of age >50 years remains unexplained and controversial. However, age should be taken into consideration if the wide excision alone without radiotherapy is being contemplated. In this setting age >50 has been associated with local recurrence.[8,38]

Histology

Several authors have described higher local failure rates following conservative surgery and radiotherapy for various histologic types. Lindberg *et al*. reported higher local failure rates for neurofibrosarcomas than for liposarcoma.[25] Higher local failure rates for non-liposarcoma was also noted by Herbert *et al*.[32] Suit *et al*. described a higher frequency of local recurrence for neurofibrosarcomas and malignant fibrous histiocytoma when analysis was limited to large tumors.[21] Angiosarcoma, malignant peripheral nerve sheath tumors and embryonal rhabdomyosarcoma were associated with an increased risk of local recurrence in comparison to liposarcoma, fibrosarcoma and non-embryonal rhabdomyosarcoma in a review of prognostic factors for local recurrence from Memorial Sloan Kettering.[33] In a more recent analysis of prognostic factors in 1041 patients from Memorial Sloan Kettering,

malignant peripheral nerve sheath tumor histology emerged as an independent prognostic factor for local recurrence and lower disease-specific survival.[34] Other institutions have not been able to identify histologic type of sarcomas as an independent predictor of local failure.[4,7,23,31,40,41]

Grade

Following WLE alone, the risk of local recurrence increases, and the time to local recurrence decreases, with increasing histologic grade.[46] Although grade clearly impacts disease-free and overall survival, the influence of tumor grade on local control following postoperative radiation is not without controversy. Most authors describe superior local control for grade I tumors in comparison to grade II or grade III sarcomas.[10,15,21,25,28,29,33,42,47] Suit *et al*. reported 0/23 local recurrences for grade I sarcomas versus a 17% local recurrence rate for grade II and III lesions following resection and postoperative radiation and postoperative radiation.[21] Lindberg *et al*. reported significantly fewer local recurrences among grade I tumors.[25] Zero local recurrences for grade I sarcomas following excision and postoperative radiation have been reported from several centers.[7,10,15] Multivariate analysis of factors affecting local control identified tumor grade as an independent predictor of local recurrence in series from Germany, France, the Netherlands, Canada and Memorial Sloan Kettering.[28,29,33,42,47] However, reports from Fox Chase Cancer Center and the Malinkrodt Institute of Radiology fail to identify grade as a factor prognostic for local control.[30,48] Indeed, in a multivariate analysis reported by Potter *et al.* from NCI, and in an updated multivariate analysis by Pisters *et al*. from Memorial Sloan Kettering, tumor grade was not identified as a predictor of local control.[23,34] It is conceivable that differences in the surgical policies for WLE and/or duration of follow-up might explain the conflicting data on the importance of tumor grade in maintaining local control. This controversy is compounded by the observation that local control following resection and brachytherapy was less favorable in low-grade tumors treated at Memorial Sloan Kettering[48,49] (see below). Although by no means a settled issue, it appears that the rate of local recurrence following conservative surgery and radiation appears to increase with increasing grade; and the increase in local recurrence for high-grade tumors can be reduced by more aggressive treatment (i.e. more extensive surgery, the use of adjuvant chemotherapy).

Location/Depth

Tumor location has been shown to affect local control, risk of metastases and survival.[35,38] Retroperitoneal tumors have by far the worst local failure rates and are associated with the poorest survival.[42,51,52] Lindberg *et al*. described significantly fewer local recurrences for primaries of the upper extremity compared to those in the abdomen.[25] Coindre *et al*. reviewed prognostic factors for 546 patients with soft-tissue sarcomas, 57% of which received postoperative radiotherapy. Local recurrence-free survival was greater for tumors arising in a limb compared to tumors arising in retroperitoneal, intra-abdominal and pelvic sites.[42]

The prognostic importance of tumor location on the extremity has been reported by several investigators. Suit *et al*. found that distal location in an extremity (i.e. at or below the elbow or knee) was associated with improved local control.[20,21] Others have found no association between tumor site on the extremity and local control.[23,28,29,32–34,43,44,48,53]

Although tumor depth has been reported by several investigators to impact disease-free and overall survival,[29,33,36,42] less attention has focused on the implication of tumor depth for local control. Tumor depth was of borderline significance in predicting local control in a series of 156 patients from the Netherlands Cancer Institute.[29] In a multivariate analysis of 546 patients from the French federation of cancer centers sarcoma group, Coindre and co-workers reported that deep tumors were associated with higher local failure in univariate, but not multivariate, analysis. In that analysis, significantly more patients with deep tumors received postoperative radiation than did patients with superficial tumors, underscoring the importance of radiotherapy in controlling deep soft-tissue sarcomas.[42] However, tumor site and depth are often interdependent with other prognostic factors, as was shown by Mandard *et al*. Superficial site was linked to other favorable prognostic factors such as small tumor size, intercompartmental location, adequate excision and absence of necrosis or blood vessel invasion. Deep location was linked to large tumor size, extracompartmental tumors, incomplete excision and high mitotic rate. When adjustment was made to correct for independent variables, tumor depth was no longer an independent variable.[45] Peabody *et al*. evaluated the prognostic importance of tumor depth in patients with soft-tissue sarcomas. Local recurrence was seen in 1/52 superficial tumors and 8/120 deep tumors. A Cox proportional-hazards model revealed that tumor depth was not a significant prognostic factor. However, tumor size and grade were significant prognostic factors.[54]

Gaynor *et al.* found deep location to be a prognostic factor for local recurrence in a univariate analysis. However, deep location was significantly associated with inadequate surgical margin, which was a significant predictor of local recurrence in a Cox analysis.[35] Indeed,

several multivariate analyses have failed to identify tumor depth as a significant independent prognostic factor for local control.[33,34,47,53]

Size

Tumor size and grade are important predictors of metastatic risk and survival. However, the importance of tumor size in obtaining local control is, at best, less certain. Tumor size is less likely to be important for local control with meticulous surgical and radiotherapy technique. Suit *et al*. reported an 8% local recurrence frequency for tumors <5 cm compared to 18% in tumors >5 cm, although this difference was not significant.[21] In an additional 13 reports, size was not important in predicting local failure following resection and postoperative radiation.[23,28–33,35,41,43,44,53,55] Thus tumor size appears not to be independently predictive of local recurrence with adequate surgery and postoperative radiation.

Margins

The pathologic margin is one of the most powerful predictors of local failure following surgery and postoperative radiotherapy of soft tissue sarcoma. Despite this fact there are no uniformly applied standards for analysis or reporting of the status of resection margins. Reported results range from subjective assessments of the adequacy of resection[55] to the "visualization" of gross disease at the time of surgery, to actual histopathologic assessments described in pathologic reports.[56] The non-uniformity in the pathologic reporting of soft-tissue sarcomas has resulted in the proposal of a minimum set of voluntary guidelines.[57] Pao and Pilepich reported on 50 patients treated with resection and post-operative radiotherapy at the Malinkodt Institute of Radiology.[47] All 11 patients who developed local recurrence had gross residual disease or positive margins. In a subsequent report from that institution, Fagundes *et al*. obtained local control in 91% (9% local failure) of patients with negative margins, compared to only 61% (39% local failure) of patients with positive margins.[58]

Bell *et al*. analyzed results of 100 patients treated at Princess Margaret Hospital in Toronto with surgical resection and postoperative radiotherapy and found that the only factor independently predictive of local recurrence was whether the surgical margin was positive ($p = 0.0004$).[59] In a subsequent report from Princess Margaret, LeVay *et al*. demonstrated that the rate of recurrence increases following WLE and postoperative radiation with increasing amounts of residual tumor. The recurrence rate for negative margins was 7%, for close margins 17%, for microscopically positive margins 22%, and for grossly positive margins 77%. Grossly positive margins was the only independent predictor of local failure in multivariate analysis ($p = 0.001$).[37]

Positive margins, or incomplete resections, have been identified as predictors of local recurrence following conservative surgery and postoperative radiation in more than a dozen reports.[29,31–33,40,41,43–45,47,48,53,56,58,59] However, several reports failed to detect an influence of surgical margins on local control when adjuvant chemotherapy was given for high-grade sarcoma.[4,23,24]

An inadequate initial operation for an unsuspected malignant sarcoma is a frequent cause of positive margins or incomplete resection. Giuliano and Eilber reviewed 90 patients referred to UCLA following initial unplanned excision of soft-tissue sarcoma. Microscopic residual tumor was found in 45% of re-excision specimens following initially inadequate surgery.[60] Zoring *et al*. reported residual tumor in 45% of re-excision specimens following initially inadequate surgery.[56] Noria *et al*. identified residual disease in 35% of patients following unplanned excision. They could not identify factors which could be associated with an increased risk of residual disease following initial unplanned resection.[61] Karakousis *et al*. found residual microscopic tumor in 91% of re-excision specimens in patients initially referred to with "complete" excisions.[10]

Radiotherapy has been shown to reduce the risk of local recurrence following an initial inadequate surgery, and it improves local control in the setting of positive margins following re-excision.[56,60] Liebel *et al*. demonstrated that 22 out of 23 patients undergoing conservative surgery and radiation had positive microscopic margins or small amounts of residual disease, and only 3/22 (14%) developed local recurrence compared to 12/16 (75%) nonirradiated patients with residual disease following conservative excision.[15]

Positive resection margins reduce local control following excision and postoperative radiation by 18-64% (average 32%).[30–32,34,41,43–45,47,53,55,58,59] Whenever possible, re-excision should be performed to achieve negative margins. Re-excision is particularly important in the setting of an unplanned excision of a malignant sarcoma. In this setting the risk of residual disease is at least 40–50%, and post-re-excision radiotherapy can reduce the risk of local recurrence by 9–60%.[15,56] Davis *et al*. analyzed 239 patients with soft-tissue sarcomas who received excision and radiotherapy. One hundred and four patients presented after an unplanned excision of sarcoma and then had re-excision of the surgical site. Tumor was found in the re-excision specimen in 42/104 (40%). Local control was significantly reduced in patients with positive margins after definite resection ($p < 0.001$), and in patients with microscopic disease in re-excision specimens ($p = 0.05$). The

frequency of margin positivity in re-excision specimens was not described.[62] Unplanned excision should be avoided whenever possible.

Recurrence following resection

Local recurrence following previous resection has been associated with an increased risk of local failure following definitive re-excision with or without postoperative radiation. The reasons for this observation are poorly understood. An underestimation of the geographic extent (geographic miss) is not likely given that most recurrences of this nature are in field.[28] Underestimation of the extent of tumor at the second excision is possible if the planes of the previous resection are not completely appreciated. It is perhaps hardest to resist the notion that local recurrence following resection results in selection of biologic (invasiveness) and tumor environmental (hypoxia) factors which make local control less likely.

Dinges *et al*. at the University of Essen, Germany, obtained local control in 94% and 91% of T1 and T2 primary tumors, compared to 55% and 61% for T1 and T2 recurrent tumors ($p = 0.0002$), respectively, following surgery and postoperative radiation. Multivariate analysis identified recurrent tumor at presentation as an independent predictor of local failure. This was despite the fact that tumors in the recurrent group were significantly smaller (4.5 cm versus 8.0 cm).[28] Previous local recurrence was also identified by Singer *et al*. to confer a higher subsequent local failure rate (47%) than nonrecurrent tumors (11%) following definitive treatment with resection with or without radiation ($p = 0.0001$).[40] Reports from MD Anderson by Zagars *et al*.[43,44] and Pollak *et al*. [31] also identified locally recurrent tumor at presentation as an adverse predictor of local control in multivariate analyses (local control was only 58–65% at 5 years for tumors presenting as recurrent). Similar findings were reported for surgically treated patients by investigators from Memorial Sloan Kettering Cancer Center.[33–35]

However, prior local failure has not always been shown to predict local recurrence when adjuvant radiotherapy is employed. There was no difference in local control for primary or locally recurrent tumors following radiotherapy in the series from Amsterdam reported by Keus *et al*.[29] Similar rates of local control for primary (75%) and locally recurrent tumors (78%) were obtained at the Princess Margaret Hospital following radiotherapy despite a higher rate of distant failure 42% versus 30%, and worse cause-specific survival for recurrent tumors.[37] Although there are no randomized trials which clearly demonstrate improved local control for locally recurrent tumors receiving postoperative radiotherapy, single-institution retrospective series suggest that the use of postoperative radiotherapy can produce local control rates similar to those obtained following treatment of primary tumors. Therefore, locally recurrent tumor is an indication for postoperative radiotherapy following re-excision.

Volume

The radiotherapy treatment volume remains an area of continued interest and controversy. Initial experience in the postoperative treatment of sarcoma led to the prescription of fields which often extended from origin to insertion of the affected muscle group.[16] Over time, improvements in resection techniques and medical imaging have allowed the radiotherapy treatment volume to be progressively reduced in size. As discussed below, excellent local control of high-grade sarcoma has been obtained with brachytherapy treatment of the tumor bed alone.[50,63]

Following postoperative external beam radiation, Pao and Pilepich noted 44% local failure with limited radiation volumes (< 5 cm), compared to 10% with subcompartmental volumes, and to 19% when the entire compartment was treated. They recommended longitudinal treatment volumes of at least 5 cm.[47] Mundt *et al*. described local control of only 30.4% of patients treated with postoperative external-beam volumes < 5 cm, compared to 93.2% local control for field margins ≥ 5 cm. No additional benefit was observed for target volumes with margins which exceeded 10 cm.[6] In the absence of data from a randomized trial demonstrating the equivalent outcome for target volumes less than and greater than 5 cm, volumes ≥ 5 cm should be used in the adjuvant radiotherapy of soft-tissue sarcomas. There is no *proven* indication for target volume reductions in the treatment of low-grade sarcomas.

Dose

Soft-tissue sarcomas can be controlled with moderately high doses of radiation (60–63 Gy) when administered in the postoperative setting.[64] Retrospective evidence of a dose–response relationship for local control has been reported.[28,30] Dignes found that, for dose ranges of <50 Gy, 50–60 Gy and >65 Gy, local failure occurred in 31%, 16% and 0%, respectively. Multivariate analysis identified total radiation dose as an independent predictor of local control. However, patients in the lowest dose ranges may have had other risk factors for recurrence (i.e. previous radiation, intra-abdominal or retroperitoneal sites, poor overall condition, etc.).[28]

Sixty-seven patients treated at Fox Chase/University of Pennsylvania received limb-sparing surgery and postoperative radiation for soft-tissue sarcomas. Overall, actuarial local control at 5 years was 87%. For

patients who received ≤ 62.5 Gy, 82% were locally controlled compared to 97% of patients who received ≥ 62.5 Gy despite there being larger tumors and a higher percentage of high-grade lesions in the group receiving ≥ 62.5 Gy. Multivariate analysis confirmed total dose > 62.5 Gy, as an independent predictor of local control.[30] In a retrospective study from the University of Miami, investigators reported an increase in survival associated with increasing radiation dose, although local control was not analyzed separately.[65] The available data suggest that total doses less than 63 Gy may compromise local control when radiation is given postoperatively for soft tissue sarcomas.

Preoperative Radiotherapy for Soft-tissue Sarcoma

The optimal sequencing of surgery and radiation in the local treatment of soft-tissue sarcomas has not been resolved. Although the majority of patients treated outside of specialized centers such as Massachusetts General Hospital or UCLA receive postoperative radiation, preoperative radiation has been shown to be a very effective adjuvant to surgery,[22,66–68] and has certain advantages which are detailed in Table 5.9.

Early experiences with pre-operative radiation were reported by McNeer *et al*.[19] From 1935 to 1959 a total of 46 patients received preoperative radiotherapy at Memorial Sloan Kettering. Preoperative radiation was used to shrink bulky tumors in order to facilitate their resection, while surgery only was used for smaller, more favorable tumors which could be resected with wide margin. Postoperative radiation was used if the margins of resection were positive. McNeer *et al*.'s local control for liposarcoma was 75% following preoperative radiation and resection, and 79% following surgery alone. In contrast, local control following postoperative radiotherapy for liposarcoma was only 57%.[19]

Preoperative radiation and concurrent infusional chemotherapy was investigated at UCLA by Eilber and colleagues.[66,69–72] In their initial experience 14 patients were treated with intra-arterial infusion of Adriamycin (20–30 mg) every 24 h for 3 days, followed by 350 cGy per day for 10 days for a total of 3500 cGy. One week following completion of radiotherapy, en-bloc resection was performed. Tumor necrosis was seen in 88% of resected specimens given intra-arterial chemotherapy and radiation, versus 63% following intra-arterial chemotherapy alone. Thirteen of 14 patients had sufficient shrinkage of tumor following preoperative radiation to allow resection. All 13 were locally controlled (local control 93%). This was in contrast to the 50% local control following surgery alone in the same report.[70] Eilber *et al*. updated the UCLA experience in 1984 having treated 100 soft-tissue sarcomas and 83 bone sarcomas. They reported local control rates of 97% in both groups. The observed complications included arterial thrombus (two patients), wound slough (13 patients), pathologic fractures (five patients), lymph edema (four patients), fibrosis and pyarthosis (one patient each). Fifty-six percent of bone allografts required revision, and complications of the endoprosthesis occurred in 9%. The overall complication rate in 77 patients with high-grade sarcoma was approximately 30% and the overall local recurrence rate was 9%.[66] A second UCLA trial addressed the high rate of complication by reducing the total radiation dose to 1750 (five fractions of 350 Gy each). This resulted in an overall reduction of complications to 25%, and a doubling of the local failure rate (i.e. 20%). The third trial randomized patients to intravenous or intra-arterial Adriamycin, with preoperative radiation to 2800 Gy in eight fractions. Local failure decreased to 14% and there was no difference in control or overall survival rate between intravenous and intra-arterial

Table 5.9 Pros and cons of preoperative radiation

	Preoperative radiation	*Postoperative radiation*
Advantage	May improve resectability	Fewer wound complications
	Radiated target volume is smaller	Immediate removal of tumor
	Improves local control for larger tumors	Histologic analysis is facilitated
	Extent of resection may be reduced	Precise assessment of tumor extent
	Decreased risk of tumor implantation	
Disadvantage	Increased postoperative complications	Radiated target volume is larger
	Diagnosis is based on limited biopsy material	Radiation is delayed
	Surgery is delayed during radiation	Amputation may be more frequent
	Tumor extent may be difficult to assess	

chemotherapy. The next two trials evaluated intravenous Adriamycin plus cisplatin (trial 4) and intravenous high-dose ifosfamide for two cycles followed by Adriamycin and cisplatin (trial 5). Both of these later two trials utilized 2800 cGy in eight fractions of 350 cGy. Local failure rates for trials 4 and 5 were 12% and 2%, respectively[72] (see Table D).

In the most recent analysis a total of 150 patients have been treated with intravenous ifosfamide, Adriamycin, and cisplatin followed by 2800 cGy and WLE. There have been only five local failures (5/150) for a local control rate of 145/150 (96%) (F. Eilber, personal communication, June 1999). These updated results are currently under preparation for publication. The UCLA trials are summarized in Table 5.10.

Using very similar techniques, investigators at UC Davis treated 25 patients (17 soft-tissue sarcomas and eight bone sarcomas) with preoperative intra-arterial infusion and radiotherapy. Twelve patients received 35 Gy in 10 fractions and 13 patients received 40 Gy in 20 fractions. There were no local in-field recurrences. Roughly 35% of patients developed wound complications. The limb salvage rate for soft-tissue sarcomas was 88% (15/17), and for bone sarcomas it was 75% (6/8).[73] Wanebo *et al*. reported a tricenter trial of intra-arterial Adriamycin and preoperative radiation (30–40 Gy) in 10–25 fractions in 66 patients with extremity sarcomas. There was only 1/66 local recurrence (1.5%). Wound complications occurred in 41%.[74]

The use of preoperative radiation without chemotherapy has been popularized by Suit and co-workers.[22,75,76] When chemotherapy is not used, patients receive approximately 50 Gy to the intact tumor with 5–10 cm longitudinal margin. Resection is carried out 2–3 weeks post-radiation. If the margins are microscopically or grossly positive a postoperative boost dose of 10–25 Gy is delivered to the site of margin positivity within the tumor bed. In early reports a postoperative boost of 14–16 Gy was routinely employed regardless of margin status.[22,75] In a more recent report the 10-year actuarial local control following preoperative radiation was 92% (see Table 5.11).[76]

High rates of local control have been reported by others employing preoperative radiotherapy and resection. Karolinska investigators treated 23 patients with preoperative radiation to 40 Gy (two patients received 64 Gy and 76 Gy, respectively), with only 2/23 local failures, one of which was successfully salvaged (ultimate LC = 22/23).[68] Barkley *et al*. reported 110 patients who received preoperative radiotherapy and resection at MD Anderson Hospital between 1970 and 1984. Doses ranged from 43 to 60 Gy in 180–200 cGy fractions. Eight patients received neutron irradiation totaling 45–58 cobalt Gray equivalent (CGyE). Local control for the group was 90% (11/110 patients failed locally).[77]

Brant *et al*. at the University of Florida at Gainsville treated 58 adult soft-tissue sarcomas of the extremities and trunk with preoperative radiation in 120–125 cGy per fraction twice daily (49/54 patients) to a total dose of 50–60 Gy (median 50.4 Gy). Ninety percent of lesions were high grade, 78% were >10 cm and 84% were extracompartmental. Local control was observed in 53/58 (91%). Local failure was higher following positive margins (33%), and for truncal lesions (17%). Eighty-seven percent retained a functional limb.[78]

Mullen and Zagars reported equivalent results with 49.8 Gy given preoperatively to larger tumors compared to 62 Gy given postoperatively to smaller tumors in patients with synovial sarcoma, suggesting that a preoperative dose of approximately 50 Gy may be a preferable strategy for larger tumors.[79] In contrast to other reported results, investigators at the University of Minnesota found no local control benefit from preoperative radiation. They reported a significantly higher complication rate associated with preoperative radiation ($p = 0.0014$).[80]

Two studies have evaluated the importance of surgical margins on local control following preoperative radiation. Sadoski *et al*. analyzed 132 patients

Table 5.10 Summary of UCLA trials of preoperative chemoradiation for soft-tissue sarcoma (from ref. 72)

Trial	*No. of patients*	*Chemotherapy*	*Fractionation schedule*	*Total radiation dose (cGy)*	*Local control*
1	77	IA Adria	350 cGy × 10	3500	91%
2	137	IA Adria	350 cGy × 5	1750	80%
3	112	IA Adria	350 cGy × 8	2800	86%
4	46	IV, Adria, Plat	350 cGy × 8	2800	88%
5	63	IV, Adria, Plat, IFOS	350 cGy × 8	2800	98%

IA = intra-arterial; IV = intravenous; Adria = Adriamycin – (30 mg/day × 3 days); IFOS – ifosfamide – (2 g/m^2 × 8 days); Plat = cisplatin – (120 mg/m^2).

Table 5.11 Results of preoperative radiation from Massachusetts General Hospital (from ref. 76)

Tumor size	*No. of patients*	*Local control*
2.5 cm	11	80%
2.6–4.9 cm	16	100%
5.0–10.0 cm	63	93%
10.1–15 cm	34	100%
15.1–20 cm	25	79%
>20 cm	11	100%
Total	160	92%

from Massachusetts General Hospital who were treated with preoperative radiotherapy. Local control was achieved in 94%. Local control with negative margins was 97%, while it was only 82% for margin-positive patients ($p = 0.02$). The size of the surgical margin following preoperative radiation had no significant influence on local control (94% for margins ≤ 1 mm, 97% for margins >1 mm, and 100% local control for no tumor in the specimen). Other factors affecting local control in margin-positive patients were: tumor location (upper versus lower extremity) and tumor grade. The authors concluded that little is gained by achieving widely negative margins following preoperative radiation.[81]

Tanabe *et al*. reviewed 95 patients who received preoperative radiation at MD Anderson Hospital. Twenty-four of 95 (26%) patients had microscopically positive margins. Local control in margin-negative patients was 91%, while it was 62% when the margins were positive ($p = 0.005$). A Cox model of factors prognostic for local recurrence identified intraoperative tumor violation and positive margins as predictors of local failure.[82]

An advantage of preoperative radiation is the potential reduction in irradiated volume. This is because the surgically manipulated or operatively exposed tissues must be included in the postoperative radiation target volume. Theoretically, the less extensive (smaller) volumes utilized with preoperative irradiation should reduce chronic radiation-related morbidity. This was evaluated by Nielsen and colleagues, who demonstrated that the radiation field size and the number of joints radiated were significantly less with preoperative, compared to postoperative radiotherapy ($p = <0.001$).[83]

The major practical disadvantage of preoperative compared to postoperative radiation is its impact on perioperative wound morbidity. Bujko and colleagues reported delays in wound healing in 37% of patients following preoperative radiation. Sixteen percent of patients required a second surgical revision for treatment of wound complications and 3% required amputation. Factors predictive of wound complications in multivariate analysis included lower versus upper extremity location, estimated blood loss >1 liter, increasing patient age, and bid fractionation.[84]

A randomized Canadian trial of preoperative versus postradiotherapy for soft-tissue sarcoma accrued patients from 1994 to 1997. The study was closed to accrual when preliminary analysis revealed a significantly increased number of wound complications in the preoperative group (35%) compared to the postoperative group (17%). This trial, which has been reported in abstract form only, has so far revealed no difference in local control or disease-free survival for preoperative versus postoperative radiotherapy.[85]

Complication rates for preoperative radiotherapy reported by various authors range from 10% to 41%.[68,72,74,78,80,82,85] The risk of perioperative wound complications is increased with preoperative radiation, despite the smaller target volumes which are radiated. However, a comparison of radiation-induced late effects (i.e. fibrosis, edema and joint dysfunction) among preoperative and postoperative patients has not yet been reported. Despite an increase in wound complications, preoperative radiation appears to improve resectability of bulky tumors,[19,76] improve local control for tumors >15 cm,[76] reduce the extent of surgery required to achieve adequate negative margins,[81] and reduce the volume of normal tissue which requires radiotherapy.[83]

Brachytherapy

Brachytherapy (*brachus*, the Greek root meaning short) is the use of radioactive sources placed close to, or implanted within, the tumor. Radiation implants, or brachytherapy, can be temporary or permanent. Brachytherapy for soft–tissue sarcomas has been used in conjunction with surgery alone, or with surgery and external beam irradiation.[49,86–88] The most frequently used technique for the treatment of soft-tissue sarcoma employs plastic catheters which are temporarily implanted into the tumor bed at the time of wide local excision (WLE). After closure of the wound the radioactive 192-iridium or high-activity 125-iodine sources are "after loaded" into the catheters and left in place until the prescribed dose of radiation has been delivered to the tumor bed. Of the several brachytherapy advantages, perhaps the most important is the ability to deliver high doses to the tumor bed while sparing normal tissue 2–3 cm away. Other advantages include: (a) the potential to eliminate the need for 6–7 weeks of outpatient radiotherapy, resulting in a shorter

overall treatment time; (b) treatment is initiated early in the postoperative period, reducing the probability of tumor proliferation, or development of chronic hypoxia which could increase the risk of local recurrence; (c) previously irradiated sites can be safely retreated as a result of the steep dose gradient which allows sparing of nearby normal tissue.

Through a series of clinical studies over the past 25 years, investigators at Memorial Sloan Kettering have documented the development of several technical refinements in brachytherapy for soft-tissue sarcomas, and have established brachytherapy as an attractive alternative to external-beam radiation in adjuvant treatment of high-grade soft-tissue sarcomas. Shiu *et al*. reported an early experience at Memorial with brachytherapy and function-sparing resection for extremity sarcomas. Thirty-three patients were reported, 16 of whom presented with recurrent tumor following previous resection. The medium dose delivered via brachytherapy equaled 4000 cGy over 4–5 days. Five patients also received 2000–4000 cGy of supplementary external-beam irradiation over 2–3 weeks postoperatively, and six patients received adjuvant chemotherapy. Local control was achieved in 100% of patients with no prior recurrence and in 10/16 (62.5%) patients with prior recurrences (overall local failure rate = 18%). Thirty-nine percent (13/33) of patients required amputation as a result of treatment complications. Factors related to complications appeared to be high brachytherapy dose (> 5000 Gy) in patients who had received prior radiotherapy (as occurred in the two patients requiring amputation) and suboptimal surgical technique (i.e. poorly vascularized flaps; closure under tension.[89]

An early comprehensive analysis of brachytherapy-related morbidity revealed a significantly increased rate of major and moderate wound complications following brachytherapy (44%) compared to resection alone (14%).[90] This observation led to several changes in surgical policy,[91] including the use of thick, vascularized flaps, or myocutaneous flaps, and soft-tissue rotation. In addition, radiation sources were after-loaded on the 5th postoperative day to prevent radiation-induced inhibition of wound healing, and attempts were made to limit the radiation dose to healing skin. In a subsequent analysis after implementation of these changes, Ormsby *et al*. reported a significant reduction in wound complications from brachytherapy (down to 14%) when radioactive sources were loaded after the 5th postoperative day, indicating that the timing of source loading is a major factor in brachytherapy-induced wound complications, and that radiation-induced delays in wound closure could be averted by allowing an initial period of wound healing.[92] These refinements in brachytherapy technique are outlined in Table 5.12.

While postoperative treatment of sarcomas with brachytherapy alone has been emphasized at Memorial Sloan Kettering, other institutions have utilized brachytherapy as a local boost given in combination with external-beam irradiation. Twenty-five patients with soft-tissue sarcomas were treated with WLE and brachytherapy (nine patients) or WLE, brachytherapy and external-beam radiotherapy (16 patients), at the University of Kansas. Local failure occurred in 5/25 (20%). The only variable identified in a multivariate analysis to predict an increased risk of local recurrence was the ratio of target volume receiving 6500 cGy divided by the tumor volume (TV65/TV). Local recurrence was increased when this volume was less than one. Also of note was that five of seven patients with positive margins experienced local failure.[86] As found in the Memorial randomized trial (see below), the use of brachytherapy did not by itself mitigate the increased risk of local failure associated with positive surgical margins.[50,86,93]

O'Connor *et al*.[94] updated the Mayo Clinic experience with brachytherapy for sarcoma originally reported by Schray *et al*. in 1990.[87] Sixty-nine patients were reviewed, of whom 68 were evaluated with follow-up. The overall local recurrence rate was 9%. Local failures were numerically more frequent in high-grade tumors (14%), marginal resection (17%) and in tumors with previous local recurrence (29%). Wound complications were more frequent when preoperative radiation was combined with resection and brachytherapy (24%) compared to resection, brachytherapy and postoperative external-beam radiation (15%). Overall local control rates (91%) and wound complication rates (17%) were comparable to resection and brachytherapy alone.[94]

Table 5.12 Refinements in surgical and brachytherapy technique developed at Memorial Sloan Kettering 1975–1996

Surgery
1. Meticulous tension-free closure of skin flaps
2. Use of thick vascularized flaps for closure of soft-tissue defects
3. Use of rotational flaps for closure of soft-tissue defects

Brachytherapy
1. Delay loading of radioactivity until the 6th postoperative day
2. Monitor dosimetry and limit dose to skin to less than 2000 cGy
3. High activity^{125} iodine seeds with less energetic photon (lower radiation exposure of normal tissues and health-care workers)
4. High dose rate after loading
5. Three-dimensional brachytherapy treatment planning

The only randomized trial of brachytherapy in the treatment of soft-tissue sarcomas was conducted at Memorial Sloan Kettering from 1982 to 1987. Long-term results of this study were reported by Pisters *et al*.[48] and Harrison *et al*.[49] One hundred and sixty-four patients with soft-tissue sarcomas were randomized after stratification by age, histology, size, depth, location, margin, and status of the primary to brachytherapy (78 patients) or surgery alone (86 patients). Randomization occurred in the operating room after a grossly complete limb-sparing resection. Patients typically received a median dose of 4500 cGy prescribed to a point in tissue 0.5 cm away from the target volume which consisted of tumor bed, plus 2 cm longitudinally and 1.5–2.0 cm mediolaterally. Local control was obtained in 83% (13/78 local failures) of those treated with brachytherapy, and in 71% (25/86, local failures) of those treated with surgery alone ($p < 0.04$). Actuarial freedom from local recurrence at 5 years equaled 82% for brachytherapy versus 69% for surgery alone ($p = 0.04$). When analysis was stratified by grade, an improvement in local control was not observed for low-grade tumors. However, there was a substantial improvement in local control for high-grade tumors treated with brachytherapy (89%) versus surgery alone (66%) ($p = 0.0025$). This is shown in Figure 5.3. Age >60 years was an important predictor of local recurrence for the entire group. Multivariate analysis limited to the high-grade group identified age >60 years and absence of brachytherapy as the only significant predictors of local failure. Among those patients with positive margins, local recurrences were *not* significantly reduced by brachytherapy. The use of brachytherapy had no significant influence on disease-specific survival or the risk of distant metastases.[48,49]

Involvement of neurovascular structures need not be a contraindication to brachytherapy. Forty-five patients reported by Zelefsky *et al*. had en-bloc resection of tumor off of neurovascular structures. Margins were grossly positive, microscopically positive, or <1 mm in 69%. Twenty-eight percent of patients had pathologic evidence of invasion into neurovascular structures. After-loading catheters were placed directly on neurovascular structures and a median dose of 4400 cGy delivered to the target volume. Post-implantation external-beam radiotherapy was given in 13/45 (28%). Local failure developed in 14/45 (31%). Poor implant geometry, and the non-use of post-implant external-beam radiotherapy in the setting of multiply positive margins were associated with local recurrence. Seven patients required amputation of local recurrence. Four patients (8.5%) who received a cumulative dose >90 Gy to the neurovascular bundle developed peripheral neuropathy. Thus a cumulative dose to neurovascular structures of < 90 Gy appeared to be well tolerated.[95]

Alekhteyar and colleagues at Memorial Sloan Kettering analyzed the impact of external-beam radiation in patients with positive margins following resection and brachytherapy. One hundred and five patients were reviewed, 87 received resection and

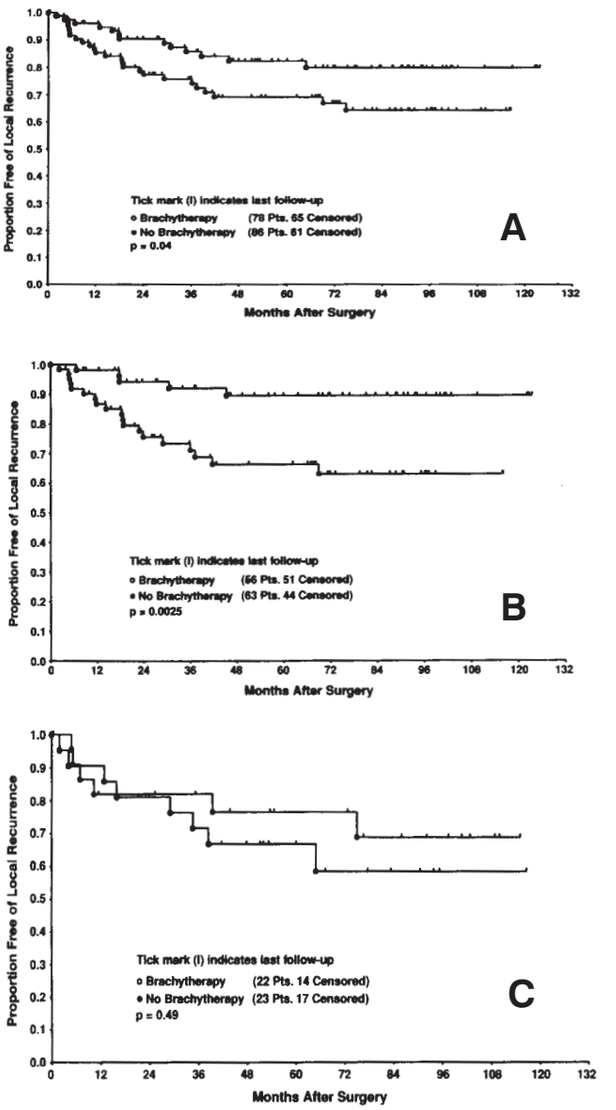


Figure 5.3 Results of the randomized trial of adjuvant brachytherapy for soft-tissue sarcoma at Memorial Sloan Kettering. Actuarial projections of freedom from local recurrence are shown for: (**A**) the entire study group; (**B**) 119 patients with high-grade sarcoma; and (**C**) 45 patients with low-grade sarcoma. There was no significant difference in freedom from local recurrence for low-grade sarcomas treated with brachytherapy. No differences were seen in distant metastasis-free survival or disease-specific survival for those patients treated with adjuvant brachytherapy (from ref. 48).

brachytherapy (45 Gy) and 18 patients received resection, brachytherapy boost (15–20 Gy) and postoperative external-beam radiation (45–50 Gy). The local control rate for the series was 86%. Local control for the brachytherapy-alone group was 82%, and for the brachytherapy radiation and external beam group it was 90% (p not significant). For patients with positive margins, local control following brachytherapy and external beam was 90% compared to 59% for brachytherapy, alone ($p = 0.08$). Multivariate analysis revealed primary tumor (nonrecurrent), and negative margins as predictive of local control. Of note were the similar rates of local control in the compared groups, despite the presence of significantly more tumors with positive margins in the brachytherapy plus external beam group (56%) compared to the brachytherapy-alone group (20%, $p = 0.003$). The authors concluded that the addition of external beam is their current policy for patients with positive margins.[96]

In summary, brachytherapy has a proven role in the treatment of soft-tissue sarcomas following WLE. It is also effective as a boost (15–20 Gy) in combination with external-beam radiotherapy (45–50 Gy). Positive margins following limb-sparing resection appear to be best managed with combined brachytherapy and external beam.[96,97] Preoperative radiation appears to increase wound complications following resection and brachytherapy.[87,94] Technical advances in brachytherapy including high dose rate after loading,[98] high activity ^{125}I,[99,100] three-dimensional treatment planning[99] and intraoperative magnetic resonance guidance are likely to improve the already good results reported in most series.[50,86,87,89,91,93–95,97–104]

Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) is the direct intraoperative application of orthovoltage X-rays or electrons to the exposed tumor, or its bed. The advantage of IORT is the ability to deliver an intraoperative boost to the surgically defined regions of interest (i.e. limited margins, gross residual tumor, etc.) while sensitive normal tissues (bowel, skin flaps, nerves, etc.) are temporarily displaced out of the irradiated field. Early forms of IORT were reported in the first decade of this century,[105] and modern IORT was developed in Japan in the 1960s and then in America at Howard University in the 1970s. IORT has been used more frequently for retroperitoneal sarcomas than for sarcomas arising in extremities or other locations. The results of IORT for retroperitoneal sarcomas will be discussed with other treatments for retroperitoneal sarcomas.

Twenty-five patients with extremity soft-tissue sarcomas received IORT at the University of Heidelberg between 1991 and 1995. A mean dose of 15 Gy was delivered intraoperatively via a dedicated linear accelerator in the operating suite capable of producing electron beam energies from 6 to 18 MeV, corresponding to the ability to penetrate tissue to depths ranging from 20 to 54 mm. All patients also received external-beam irradiation 3–6 weeks after the operation to a mean dose of 44 Gy. Local control was achieved in 92% of patients with a median follow-up of 26.8 months. One out of four patients (25%) with positive margins had local failure compared to only one out of 21 (4%) with negative margins. Three patients had wound healing complications and six patients developed severe late complications, including: pathologic fracture in two patients; limb contracture in two patients; tibial osteitis and neuropathy in one patient each. Overall and disease-free survival levels were lower for high-grade lesions, consistent with an increased risk of metastatic relapse in that group.[105] Haddock *et al*. reported 91 patients treated with IORT for extremity and limb girdle sarcomas at the Mayo Clinic from 1986 to 1995. Sixty-three patients had high-grade lesions and 28 had low-grade lesions. Tumors were located in the upper extremity in 20 patients, lower extremity in 54 patients and limb girdle in 17 patients. Seventy-four patients had primary tumors and 17 had recurrent tumors. IORT doses ranged from 7.5 to 20 Gy (median 10 Gy). Eighty-eight patients also received external-beam radiotherapy (69 received preoperative and 19 received postoperative irradiation) to a median dose of 50.4 Gy. Thirty-nine patients had microscopically positive margins (43%), 38 had close margins (42%), one patient had gross residual disease. Margins were negative in 13 patients. Local control with a median follow-up of 3 years was 92%. There were 6/91 local failures, one of which was within the IORT boost field. Overall survival at 3 years was 76%. Data describing the frequency of failure as a function of resection margin were not disclosed.[106] However, these results are quite favorable given that 78/91 patients had positive margins. Longer follow-up is needed to confirm these excellent results.

High LET and Proton Therapy

Alternative forms of radiation have been utilized in the treatment of soft-tissue sarcomas. High linear energy transfer (LET) radiation refers to those forms of radiation which produce more dense energy transfer (ionization) per unit path length in tissue. Examples of high-LET radiation include alpha particles, neutrons, neon and argon ions. The radiobiologic advantages of high-LET radiation include: (a) reduced oxygen dependence; (b) a higher yield of DNA double-strand

breaks; and (c) cell killing which is less dependent on cell cycle distribution. LET for various forms of radiation is shown diagrammatically in Figure 5.4.

Early neutron therapy trials produced higher local control rates than those achieved with X-rays; however, toxicities were also higher. Catterall treated 28 patients with 16 MeV neutrons to a total dose of 1560 neutron rads over 4 weeks. Twenty-one of 28 (75%) patients were locally controlled, yet 9/28 (32%) developed major complications.[107] The high complication rate was likely a result of the inadequate depth dose characteristics of the 16 MeV neutron beam. Higher beam energies deliver their maximum dose deeper in tissue, allowing relative sparing of skin and subcutaneous tissues.

Investigators at M.D. Anderson Hospital treated 34 patients with locally advanced, unresected sarcomas at the Texas A&M Variable Energy Cyclotron (TAMVEC). In the early years of this pilot study, patients were treated with 16 MeV neutrons, and after 1972 a higher-energy 50 MeV neutron beam was used. The higher-energy neutron beam produced a depth of maximum dose (D_{max}) of 8 mm, and at 10 cm delivered 63% of the D_{max} dose, compared to a D_{max} of 2 mm, and 41.3% of D_{max} at 10 cm with the 16 MeV beam. Local control for the 29 patients with soft-tissue sarcomas was 69%. A variety of fractionation schemes and combinations with X-ray therapy were used. Only one of four patients with chondrosarcoma was controlled and the one patient with osteosarcoma had persistent local disease following irradiation. Four patients (4/34, 11%) developed a major complication; two of these were skin ulcerations following treatment with the 16 MeV neutron beam. One patient developed a vesico-vaginal fistula following a 50 MeV neutron boost combined with 25 MeV X-rays to a total dose of 7610 rad equivalents.[108]

One hundred and ninety-nine patients with soft-tissue sarcomas were treated with neutron irradiation at the Swiss Institute of Nuclear Research (SIN). Local control for grade I, grade II, and grade III tumors was 76%, 53% and 40%. The corresponding 5-year survival rates were 77%, 63.1% and 34%. Local control was 49% for gross residual disease, 84% for microscopic disease and 95% for completely resected tumor with negative margins. Complication rates decreased from 22% to 15% when neutron irradiation was limited to a boost combined with photons, rather than used for the entire treatment. However, numerically lower rates of local control were also observed following neutron "boost" compared to neutrons alone.[109,110]

Richard reported on 75 patients with soft-tissue sarcomas treated with neutrons at the Catholic University in Belgium. Forty-seven patients were treated following "radical" resection and 28 patients had large inoperable, incompletely resected or recurrent tumors. Local

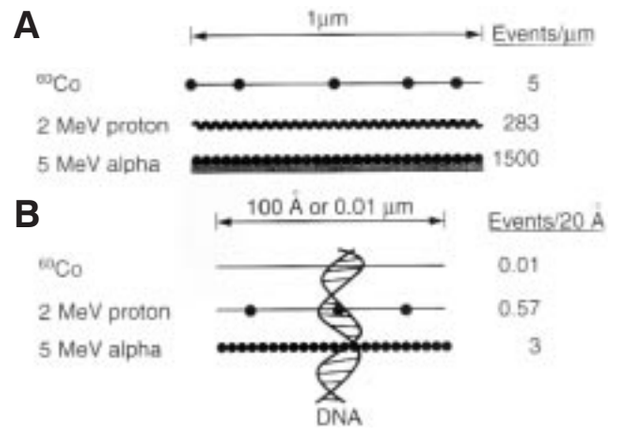


Figure 5.4 The frequency of ionization events along the tracks of various forms of radiation which markedly differ in linear energy transfer (LET). Ionization events over 1 micron (1 μm) are shown in (**A**), and events over a distance of 100 angstrom (100 Å) are shown in (**B**). The dimensions of a DNA molecule are represented by the double helix (redrawn from Tannock IF, Hill RP, editors. The Basis of Science of Oncology, 3rd edn. New York: McGraw Hill; 1998).

control rates for each group were 43/47 (92%) and 5/28 (18%), respectively.[111] Pickering *et al*. described the Hammersmith Hospital in London experience with neutrons for soft-tissue sarcomas. Sixty-six patients were retrospectively reviewed who had received 1560 neutron cGy in 12 fractions over 28 days. Fifty of the 66 patients (75%) had palpable tumor, and 31 patients had tumors >10 cm, of which more than 50% were grade 3 lesions. Local control in the 16 patients with negative margins was 94% (15/16), and the 5-year survival for this group was 86%. Complete regression was noted in 34/50 (68%) of patients with palpable gross disease. The overall local control rate for palpable tumors was 52%. Forty-one percent of patients developed late complications, mostly involving skin as a result of the poor depth of penetration of the low-energy neutron beam.[112] In a review of the world literature for fast neutron therapy for soft-tissue sarcomas, Griffin *et al*. reported a local control of 50% for patients with gross or unresectable disease.[113] These results appear superior to those reported for photon radiation alone.[15,16,20,25]

Pi-mesons (pions) are high-LET particles that share the biologic advantages of neutrons, yet also possesses the dose distribution advantages of charged particles. The Bragg peak phenomenon, characteristic of pions, protons and other charged particle radiation, is shown diagrammatically in Figure 5.5. The large deposition of ionizing energy at a discrete depth resulting from the Bragg peak produces radiation dose distributions

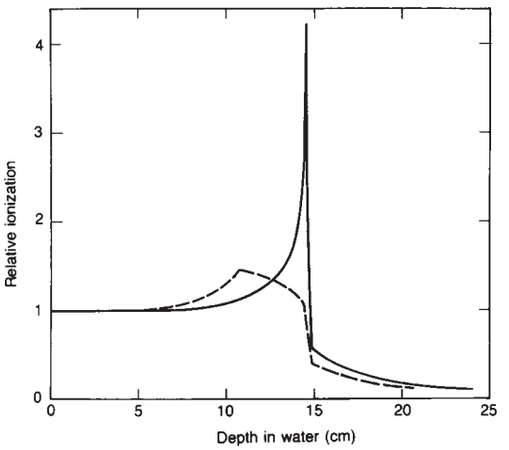


Figure 5.5 The Bragg peak is the sudden, large deposition of energy which occurs at a depth in tissue where the kinetic energy of a charged particle has been sufficiently depleted to allow a close interaction with an oppositely charged particle (i.e. an electron or proton in tissue). The characteristically sharp Bragg peak is compared to a modulated Bragg peak used for clinical treatment. Despite the spreading out of the modulated peak, a sharp decline in dose beyond a certain depth remains (redrawn from Perez C, Brady L, editors. Principles and Practice of Radiation Oncology. Philadelphia: Lippincott; 1992).

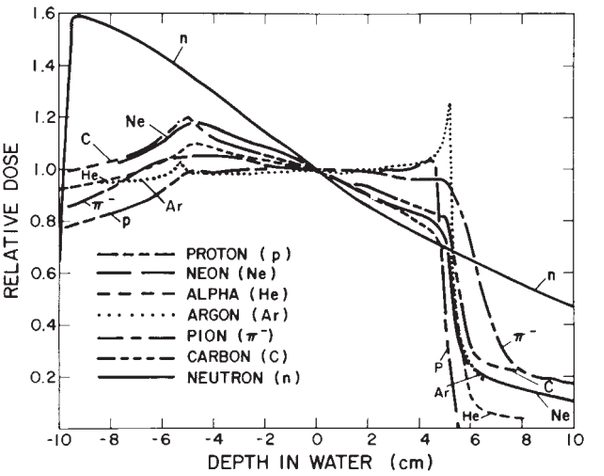


Figure 5.6 The depth dose characteristics of several heavy particle beams with modulated Bragg peaks are compared to Neutrons (n) which have depth dose characteristics similar to low-energy photons (X-rays) (redrawn from Kahn F, The Physics of Radiation Therapy, 2nd edn. Baltimore: Williams & Wilkins; 1994).

which are superior to those produced by X-rays. A comparison of depth dose characteristics of various heavy particle beams is shown in Figure 5.6. In addition to the advantage of Bragg peak dosimetry, pions possess high LET which results in more effective cell killing. Greiner *et al*. reported the Paul Sherrer (formerly SIN) Institute experience with unresectable sarcomas treated with pion radiotherapy. Thirty-five patients were treated; three following gross excision of tumor, nine following partial resections, and 15 following biopsy only. Eight patients were treated with low-dose therapy (7–27 Gy) and 27 patients received high-dose (30–36 Gy) therapy. Local control for the 27 patients in the high-dose group was 64%. Late reactions occurred in 28% of patients, and they were severe (grade III or IV) in 18%. One patient each developed skin necrosis, impaired erection, liver toxicity, leg edema and small bowel obstruction.[114] This experience compares favorably to results with conventional photon therapy alone for gross disease.[15,16,20,25]

Protons also produce Bragg peak dosimetry in tissue. The depth dose characteristics of a clinical proton beam are shown diagrammatically in Figure 5.7. Protons have biological effects which are similar to photons or X-rays; however, the dosimetry of protons resulting from the Bragg peak allows higher doses of radiation to be delivered to regions closer to critical structures. Protons have been used in the treatment of soft-tissue sarcomas

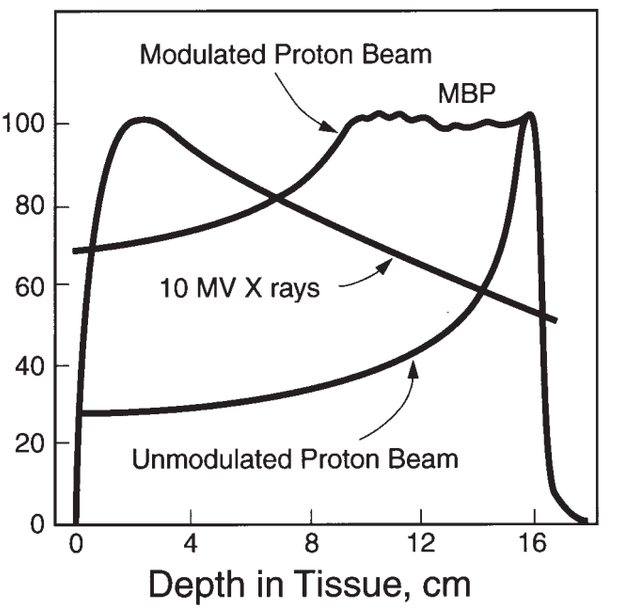


Figure 5.7 Modulated Bragg peak which is utilized for clinical proton therapy. Note that while the peak of radiation dose is spread out as a result of beam modulation, the fall-off in dose at depth remains very sharp. That is what makes charged particles so useful in treating tumors which lie very close to dose-limiting critical structures. The modulated Bragg peak (MBP) is produced to allow a homogeneous dose to be delivered within a tumor of a given thickness at a given depth in tissue. Proton beam modulators typically consist of paraffin 'tissue-equivalent' material of varying thickness, which are placed in between the beam source and the patient (redrawn from Liebel S, Phillips T, editors. Textbook of Radiation Oncology. Philadelphia: Saunders; 1998).

at Massachusetts General Hospital with local control achieved in 86%.[115] However, proton therapy has perhaps been most useful in the treatment of osteogenic or chondrogenic tumors of the skull base or axial skeleton. Hug *et al*. reported 47 patients with bone sarcoma who were treated at the Massachusetts General Hospital Harvard Cyclotron Facility with proton therapy. In this series, patients were grouped as follows: group 1 (14 chordoma and six chondrosarcoma); group 2 (15 osteogenic sarcoma); group 3 (eight giant-cell tumors, two osteoblastoma and two chondrosarcoma). Patients received proton radiation alone, or photon therapy with a proton boost (preoperatively and/or postoperatively). Seven patients were treated following biopsy only. Local control for group 1 was: 9/14 (64%) for chordomas and 6/6 (100%) chondrosarcomas. Local control for group 2 was 11/15 (73%) and local control in group 3 was 10/12 (83%). Late toxicities were similar to those experienced following conventional radiotherapy.[116]

In summary, charged particle and high-LET therapies offer promise in the treatment of unresectable soft-tissue and bone sarcomas. Improvement in beam technology will allow higher energy, more deeply penetrating beams to be produced at a lower cost with greater convenience. With optimization of dose distributions through the use of three-dimensional treatment planning and better depth dose characteristics, the results for locally advanced unresectable tumors should continue to improve.

Radiosensitizers

Many chemical agents have been shown to modify the cellular responses to radiation.[117–119] Early recognition of the importance of tumor hypoxia led to the development of agents which sensitize hypoxic cells. Hypoxic cell sensitizers were extensively tested in the 1970s and 1980s without significant improvements in local control when combined with radiation. Misonidazole, an *in-vitro* hypoxic cell sensitizer, was administered to 10 patients with sarcomas (seven osteogenic sarcoma, one low-grade, one undifferentiated and one chondrosarcoma) treated at the National Cancer Institute (NCI). Radiation was administered in 400–450 cGy fractions to a total of 40–50 Gy. There were no complete responses. Seven out of 10 (70%) patients experienced no further growth of the primary tumor during follow-up. Autopsy in one patient revealed persistent osteoid matrix and no viable tumor cell.[120]

Halogenated pyrimidines constitute a different class of radiosensitizers. These agents are incorporated into the DNA of actively cycling cells, resulting in an increase yield of DNA double-strand breaks following radiation exposure. Bromodeoxyuridine (BUDR) and iododeoxyuridine (IUDR) have been used in the treatment of soft-tissue sarcomas and osteosarcomas.[120–122] Martinez *et al*. reported high local control and high complication rates following treatment of osteosarcoma with BUDR and hypofractionated radiation (see section on osteosarcoma later in this chapter).[121]

A series of patients with soft-tissue sarcomas were treated at the NCI with halogenated pyrimidine radiosensitizers. Five patients were initially treated with BUDR and once-daily radiotherapy for unresectable soft-tissue sarcomas. Three out of five (60%) were locally controlled.[120] A second cohort of 14 patients were treated with IUDR and twice-daily radiation. Twelve of 14 (86%) were locally controlled, with six patients (43%) achieving a complete response and four others (28%) having >50% reduction in tumor size, for an overall response rate of 71%. An update of the NCI experience was reported by Goffman *et al*. Thirty-six patients with large or massive sarcomas were treated with infusional IUDR and twice-daily radiotherapy to 70–75 Gy. All lesions were considered unresectable except in two patients who refused hemipelvectomy. Four patients did not complete radiotherapy, and local control for those who did complete treatment was 62% (20/32).[122]

Preoperative radiation and infusional IUDR was studied in 37 patients with locally advanced or unresectable sarcomas at the University of Michigan. Four patients developed distant metastases shortly after treatment, and one patient was lost to follow-up. There were no complete responses and five (14%) had a partial response. Twenty-eight patients (28/37, 76%) underwent surgical resection. Thirteen out of 28 (46%) were resected with negative margins and 7/10 patients with previously unresectable extremity sarcomas were resected with negative margins. Late toxicities requiring surgical intervention developed in six patients, and one patient died of cholangitis believed to be secondary to treatment of a retrohepatic sarcoma. Overall, local control was obtained in 75% (27/36). The authors concluded that halogenated pyrimidine sensitizers improved the resectability of advanced limb and truncal sarcomas.[123] Comparisons of halogenated pyrimidine radiosensitizers to other preoperative regimens, including radiotherapy alone, warrants further study.

Razoxane (ICRF 159) is an agent which was shown over 20 years ago to hold promise as a radiosensitizer. Laboratory studies demonstrated its ability to radiosensitize tumors through blocking dividing cells at the G2/M phase of the cell cycle (the most radiosensitive phase). A randomized trial of razoxane and radiotherapy versus radiotherapy alone for soft-tissue sarcomas was initiated in 1978. Sixty-six patients were treated with radiation alone and 64 patients received radiation

and razoxane. For those patients treated postoperatively, local control was 81% (21/26) for the razoxane group, and 73% (16/22) following radiation alone. For patients treated with gross disease, local control and complete response rates were 30% and 26% following radiation only, versus 64% ($p = 0.001$) and 38% for the razoxane group. There were no significant differences in survival or late affects between treatment groups.[124]

Despite the variety of molecular targets, and the considerable resources which have been invested in the development of radiosensitizers, none has yet emerged as significant clinical adjuvants to radiotherapy. However, it is likely that the future will witness further clinical trials with drugs which specifically target signal transduction, growth factor receptors, angiogenesis, proteosome inhibition, transcriptional silencing, apoptosis, cell cycle check points, and DNA repair as mechanisms of radiosensitization. Locally advanced or unresectable soft-tissue sarcomas will remain excellent clinical models to test new strategies for radiosensitization.[124]

Retroperitoneal Sarcomas

Sarcomas of the retroperitoneum represent a unique challenge to surgeons and radiation oncologists. Despite the relative rarity of these tumors, their importance cannot be overemphasized when it is considered that the solutions to the unique problems posed by these tumors have application to other more common malignancies such as colorectal cancer, gynecological cancers and other intra-abdominal or pelvic malignancies. Retroperitoneal sarcomas (RPS) are characterized by: (a) locally advanced disease at presentation; (b) proximity to vital structures; (c) infiltrative growth; (d) frequent peritoneal dissemination; and (e) the limited radiation tolerance of adjacent normal tissues.

Pretreatment prognostic factors which affect disease-free and overall survival include: high grade, the number of mitoses, age, previous recurrence, histologic type, size >10 cm, and the presence of metastatic disease.[125–129] The most important treatment factor influencing local control and survival is the completeness of resection (i.e. status of surgical margins).[125–128,130–132] Local recurrence following surgery alone is 34–80%.[52,125,129,133,134,137] That survival is highly dependent on local control is suggested by the predominance of local failure at the time of recurrence (60% of recurrences and local) and by the presence of local recurrence in 60–100% of patients who die of disease.[136]

Radiation therapy improves local control and may change the pattern of relapse. However, radiotherapy has not been proven to increase survival. It is unlikely that local radiotherapy, in the absence of effective regional/systemic treatment, will have a major influence on survival. This is due to the propensity of RPS for regional metastases and the proximity of dose-limiting normal structures.

An early experience with radiotherapy for RPS was reported from Memorial Sloan Kettering by Kinne *et al*. Thirty-four patients were treated with complete resection ± radiation (11 patients, group I), incomplete excision plus ± radiation (15 patients, group II), and biopsy plus radiation (eight patients, group III). The disease-free interval for the group I patients was 35 months with radiation and 40 months without radiation. For group II the disease-free interval was 32 months with radiation and 16 months without radiation. There were only two long-term survivors in group III; one well-differentiated liposarcoma who was disease-free for 30 years, and one with liposarcoma who presented with local and metastatic recurrence 10 years postradiation. Nineteen of 34 (56%) patients developed metastatic disease, all of whom also had local recurrence. Although radiotherapy techniques in this series varied considerably through the years, most patients received 50 Gy for definitive treatment of gross disease, and 40 Gy as adjuvant treatment. The clearest benefit of radiotherapy seemed to be in the delay of local recurrence in those patients with partially resected tumor (group II).[132] In a second report from Memorial Sloan Kettering, by Fortner *et al*., 27 patients had complete excision of their RPS, 10 of whom received adjuvant radiation. The 5-year disease-free and overall survival rates were 30% and 50% following surgery and radiotherapy versus 12% and 12% following surgery alone.[137]

In the Massachusetts General experience, reported by Tepper *et al*., the local control and 5-year survival were 54% and 54%, respectively in 17 patients treated with curative intent. Four of six patients who received < 50 Gy developed local recurrence compared to 1/11 patients treated with > 50 Gy.[138] Harrison *et al*. reviewed 23 patients with RPS referred for radiation therapy at Yale. Out of 23 patients referred, only five had complete or partial resection. Three out of five (60%) were locally controlled at 5 years following radiotherapy. One of these three patients had a recurrence locally at 73 months.[131]

Eleven patients with RPS were treated with complete resection followed by 50–64 Gy external-beam radiotherapy at St Bartolo Hospital in Vicenza, Italy. Local control was obtained in 64% (7/11), yet 2/7 (28%) locally controlled patients developed metastatic disease. At 4 years 64% (7/11) patients are alive and 45% (5/11) are alive without disease.[139] The Netherlands Cancer Institute experience describing 34 patients treated with curative surgery ± radiation was reported

by Van Doorn *et al*. Four patients had incomplete resection leaving 30 patients with limited (22) or extended (8) surgical margins. Thirteen patients received postoperative radiation. Local recurrence with or without metastatic disease developed in 23/34 patients (68%). Ten patients developed distant metastases, all in association with local recurrence. Six of 13 (46%) who received adjuvant radiotherapy were locally controlled compared to 3/19 (16%) who did not receive radiation ($p < 0.01$).[140]

From 1975 to 1988, 104 patients with RPS were seen at the Princess Margaret Hospital in Toronto. All surgery was performed at outlying institutions. Forty-two patients had complete resection (43%), 57 patients (55%) had gross residual disease or biopsy only, and two patients had unknown extents of residual disease. Of the 42 completely resected tumors, 39 (93%) had microscopically positive margins. The median dose of radiotherapy was 40 Gy. The locoregional relapse-free rate was only 28% and 9% at 5 and 10 years, respectively. Overall survival was 36% and 14% at 5 years and 10 years, respectively. The locoregional relapse-free rate for the patients who were completely resected was 55% and 22% at 5 and 10 years, respectively. In the group of patients with complete resection, those who received radiotherapy had a prolonged median time to recurrence (103 months) compared to those who received no radiation (30 months). When the comparison was limited to tumor bed recurrences there was a significant difference between those who received radiation (36 patients) and those who did not (nine patients) ($p = 0.02$).[141] The low doses of radiation and the preponderance of positive margins and gross disease in this study bias the results against adjuvant radiotherapy, and therefore support the validity of the improvement in local control associated with radiotherapy.

Fein *et al*. reported the Fox Chase/University of Pennsylvania experience with 21 RPS patients treated from 1965 to 1992. Two patients received preoperative radiation and 19 received postoperative radiation. Brachytherapy or IORT boost was used in 5/21 patients. Radiation doses ranged from 36 to 90 Gy, with a median of 54 Gy. Margins of resection were clearly negative in one patient, close in two patients and either grossly or microscopically positive, or unknown, in the remaining patients. For patients with grossly positive margins the median radiation dose was 59.4 Gy. Follow-up ranged from 14 to 340 months. The actuarial local control at 5 years was 72%. Survival at 2 and 5 years was 69% and 44%, respectively. Local failure occurred in only 2/8 (25%) of patients who received a total dose > 55.2 Gy, compared to 5/13 (38%) of patients who received < 55.2 Gy.[134] Although these results appear encouraging, follow-up is not mature for all patients reviewed in this retrospective analysis, and locoregional failures can continue to occur for 10 years or longer.[142]

Dynamic three-dimensional conformal pion therapy was used to treat 21 RPS at the Paul Scherrer Institute in Bern, Switzerland. The median target volume treated was approximately 1000 ml and the median pion dose used was 32.3 Gy. Radiation with or without chemotherapy was used in 14 patients, and radiation plus resection was used in seven patients. The median follow-up was 24 months (range 12–75 months). Local control (described as absence of growth and control of symptoms) was obtained in 18/21 (90%) of patients. The actuarial 3- and 5-year local control was 90% and 60%, respectively. The projected 3- and 5-year survivals were 67% and 33%, respectively. Toxicities included mild enteritis during radiotherapy, leg edema, skin fibrosis, impaired hepatic function, and two cases of bowel obstruction felt to be a result of non-radiation-related complications. The limited follow-up and lack of histologic confirmation of tumor response does not allow definitive conclusions regarding the effectiveness of pion therapy for RPS.[143]

The bulk of the evidence appears to support the observation that radiation therapy improves local control in RPS. Indeed, in an analysis of prognostic factors among 48 patients with RPS who survived more than 5 years, radiation therapy was the only factor which significantly predicted a reduced risk of local recurrence.[126]

Intraoperative Radiation Therapy for RPS

In order to avoid the limitations on radiation dose escalation imposed by normal organs such a small bowel, novel techniques such as IORT have been used with mixed results in the treatment of RPS.

Willet and colleagues at Massachusetts General Hospital treated 20 RPS patients with preoperative (19 patients) or postoperative (one patient) external-beam radiation (40–50 Gy) and IORT (15 Gy for microscopic disease and 20 Gy for gross residual disease; range 10–20 Gy). Patients received 100% oxygen breathing during IORT. Of the 20 patients treated with this regimen, one patient developed metastatic disease prior to resection and was not explored, and two patients who had diffuse peritoneal sarcomatosis at laparotomy were not resected. Seventeen patients had partial or complete resection, and IORT was used in only 12 patients due to tumor bed sizes which exceeded IORT capabilities in five cases. Three of the five patients not receiving IORT were treated with postoperative radiation. The actuarial local control for the 17 patients resected with or without IORT was 81% at 4 years.

Local control was obtained in 9/12 (75%) among those patients who received IORT. Both patients with gross residual disease treated with IORT failed locally. There were no local failures in the three patients who were treated with preoperative *and* postoperative radiation without IORT. IORT-related toxicities included hydronephrosis accompanied by radiation neuropathy in two patients.[144]

Similar results were reported by Gunderson from the Mayo Clinic. Twenty patients (10 primary and 10 recurrent) received resection, IORT and preoperative or postoperative radiotherapy. Twelve were high grade and eight were low grade. Residual disease was microscopic in 11 patients and gross in nine patients. External-beam doses ranged from 45 to 60.4 Gy. IORT doses were 10–12 Gy for microscopic residual disease and 15–20 Gy for gross disease. Follow-up ranged from 9 to 69 months with a minimum of 15 months follow-up on all living patients. Local control within the irradiated sites occurred in 16/20 patients (80%). Regional failure outside of the irradiation fields occurred in two patients (10%). In total, locoregional failure occurred in 6/20 patients (30%). Metastatic failures were more numerous in primary patients (due to the higher percentage of high-grade tumors), and local failure was more frequent with recurrent tumors. The actuarial 5-year survival was 48.5%. Six patients developed significant treatment-related complications: small bowel obstruction following surgery and postoperative radiation in one patient, motor neuropathy in one patient, wound complications in two patients, a urologic complication in one patient, and fibrosis in one patient.[145]

A third pilot experience was reported by Bussieres *et al*. from Bordeaux, France. Nineteen patients with RPS received IORT: 14 with primary and five with recurrent tumors. IORT doses ranged from 15 to 20 Gy. Thirteen of 19 patients also received external-beam radiation. The median follow-up was 17 months (range 4–37 months). There were four locoregional recurrences (21%) and three (16%) patients had metastatic disease as their first site of failure. The actuarial local control and survival at 2 years was 76% and 60%, respectively. Observed complications included: lymphedema in two patients, lumbar plexopathy in one patient, chronic enteritis in two cases, and one fatal external iliac artery rupture.[146]

The three IORT pilot studies described above, while encouraging, do not clearly support the role of IORT in the treatment of RPS beyond documenting its feasibility and associated toxicities. The results described are not clearly superior to those achieved with postoperative radiation alone, and with small patient numbers and limited follow-up, conclusions are tenuous at best. Indeed Heslin *et al*. documented a continuing risk of local failure which was approximately 5% per year.[126]

Several of the issues regarding published IORT results were addressed by Sindelar *et al*. in the final results of the NCI prospective randomized trail.[147] In that study 35 patients without metastatic disease were randomized to resection and postoperative high-dose radiotherapy (20 patients), or resection, IORT and postoperative low-dose radiotherapy (15 patients). All patients received misonidazole 15–30 min prior to IORT. The IORT dose equaled 20 Gy. An actual protocol IORT treatment is shown in Figure 5.8. Postoperative low-dose radiation given to IORT patients equaled 35–40 Gy over 4–5 weeks. High-dose radiotherapy in the control arm consisted of 35–40 Gy followed by a coned-down boost for an additional 15 Gy. All patients were followed with routine examinations every 3–4 months until death. Median follow-up equaled 8 years and the minimum follow-up was 5 years. The median overall survival favored the control group (IORT 45 months; control 52 months), but the difference was not significant. Failures were scored as local ("in-field" recurrences within the abdomen or retroperitoneum region encompassed by the radiotherapy portal), locoregional (within the abdomen or retroperitoneum including diffuse peritoneal sarcomatosis), and distant. There was no significant difference in disease-free survivals between the two groups; however, IORT did have a significant impact on the pattern of disease relapse. While the median time to locoregional recurrence for the IORT group was 63 months compared to 38 months for the control group ($p = 0.4$), the time to in-field local recurrence was significantly longer in the IORT group (127 months), compared to the control group (38 months) ($p < 0.05$). The local failure rate was significantly reduced by IORT. There were 6/15 (40%) local failures with IORT compared to 16/20 (80%) in the control group ($p < 0.05$). IORT patients had a higher rate of metastatic recurrence as the first site of recurrence (50%) compared to the control group (19%). The results of this, the only randomized trial of retroperitoneal sarcomas ever published, are summarized in Table 5.13. Gastrointestinal complications were more frequent in the control group. Chronic enteritis occurred in 12 control patients and in only one IORT patient ($p < 0.01$). Neurologic complications (peripheral neuropathy) developed in nine IORT patients compared to only one control patient ($p < 0.01$). Three IORT patients treated with large IORT treatment portals in the region of femoral and sciatic nerve roots had permanent motor weakness. The authors concluded that IORT improves local control and is associated with lower gastrointestinal toxicity in comparison to conventional radiotherapy. A reduction

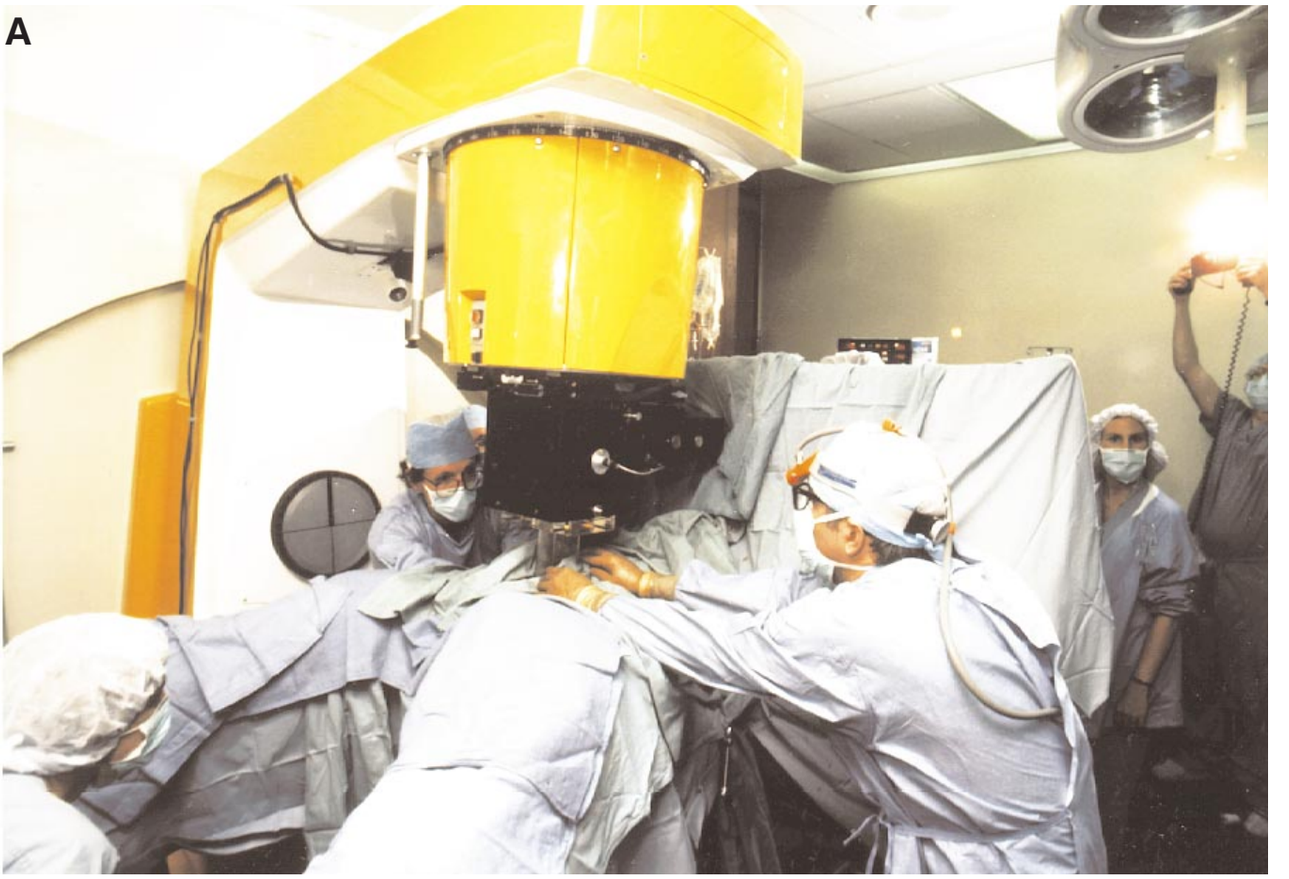


Figure 5.8 Intraoperative radiotherapy for a retroperitoneal sarcoma. In (**A**) the patient, with a lucite electron cone in place over the tumor bed, is being positioned or 'docked' below the gantry of the intraoperative accelerator immediately prior to radiation. (**B**) The patient, 'docked' in place, is receiving intraoperative radiation. While the beam is on, all health-care personnel are required to vacate the treatment vault/operating suite, including the anesthesiologist. Closed-circuit television cameras monitor life-support function and several key points including the tumor bed as viewed through the electron cone from the direction of the beam source.

in IORT dose to 15 Gy was recommended, since similar doses had not previously been associated with neuropathy.[147] In this mature study (77% of patients had died), IORT was not significantly superior to conventional radiotherapy in prolonging survival. However, IORT did change the natural history of RPS and was reasonably well tolerated. With the development of more effective systemic chemotherapy, and further progress in optimizing the clinical radiobiology of IORT to widen the differential between tumor cell kill and normal tissue toxicity, IORT could have a more standard role in the management of RPS. For now

Table 5.13 Results of a randomized trial of IORT for retroperitoneal sarcoma

	IORT	*Control*	*P-value*
Actuarial results			
Overall survival	45 months	52 months	0.39
Disease-free interval	19 months	38 months	0.58
Time to locoregional recurrence	63 months	38 months	0.40
Time to in-field local recurrence	>127 months	38 months	<0.05
Patterns of recurrence			
First sites			
Local in field	3/10	10/16	0.23
Diffuse locoregional	2/10	2/16	0.63
Distant metastases	5/10	3/16	0.19
Sites at death			
Local in field	3/10	16/16	<0.001
Diffuse locoregional	3/10	6/16	0.99
Distant metastases	5/10	6/16	0.69

IORT remains investigational.

In summary, the most important prognostic predictor of survival in patients with RPS is completeness of resection. Conventional radiotherapy has been shown to improve local control in retrospective series. However, its role has not been proven in a randomized trial. IORT can reduce, but not eliminate, the local failure of RPS. Because the dominant mode of failure and death is intra-abdominal/regional retroperitoneal relapse, development of novel approaches to locoregional therapy will continue to be an important goal in the treatment of RPS.

BONE SARCOMAS

Ewing's Sarcoma

Ewing's sarcoma is a member of a family of poorly differentiated, small, round-cell tumors, the molecular biology of which was recently reviewed.[149] Ewing's sarcoma is responsive to chemotherapy and radiation. Historically, recommendations regarding the management of Ewing's sarcoma initially de-emphasized and now re-emphasize the role of surgical resection in treatment of the primary site. While there have been no randomized comparisons of surgery and radiation for treatment of the primary site, several retrospective and nonrandomized prospective studies have documented superior local control and superior event-free survival associated with surgical resection.[149–159] With few exceptions, resection has been utilized for patients who would have a favorable outcome regardless of the form of local management. Indeed several authors have identified poor prognostic factors more frequently in patients treated primarily with radiation.[153,156,158,160]

The contemporary treatment of Ewing's sarcoma has as its cornerstone multi-agent chemotherapy containing Adriamycin. Management of the local tumor is individualized. Surgery is favored for expendable bones and whenever possible as long as organ and limb functional integrity are preserved. In all other circumstances local control with good to excellent functional results can be achieved in 70–100% of cases with induction chemotherapy and optimal radiotherapy techniques.[161–168] Recognition of the patterns of local failure and the need to reduce the risk of radiation late effects, including second cancers, continue to stimulate efforts to refine radiotherapy doses and volumes.[155,157]

Radiotherapy has been the dominant treatment of Ewing's sarcoma for most of this century. James Ewing's initial description of "diffuse endothelomia of bone" in 1921 noted the responsiveness of this tumor to radium treatment.[169] This was further demonstrated by C. C. Wang, who reported 50 patients with Ewing's sarcoma treated at the Massachusetts General Hospital from 1930 to 1952. Local control was obtained with radiation alone in 15/22 (68%) patients, and four patients (18%) treated with curative intent survived without disease for 6–13 years.[1] In the University of California San Francisco experience from 1935 to 1970, reported by Phillips and colleagues, 13/16 (72%) of patients were locally controlled with radiation alone, and 24% survived 5 years or longer.[2] These series, which predate the discovery of effective chemotherapy and the development of limb-sparing surgical procedures, clearly documented the effectiveness of radiation as an alternative to amputation in the 70–80% of patients who would eventually have succumbed to metastatic disease, and as a curative treatment in approximately 20% of patients without metastases. The practice of irradiating the entire bone, and the use of tumor doses above 5000 rad, resulted from these early experiences.[1,2,170]

The development of effective chemotherapy regimes in the 1970s ushered in a new era in the treatment of Ewing's sarcoma. This was accompanied by refinements in surgical limb-sparing techniques for bone tumors. Multiagent chemotherapy improved 5-year survival (60% with Adriamycin-containing chemotherapy in the first Intergroup Ewing's Sarcoma Study (IESS-I) compared to 18–24% without chemotherapy) as well as local control.[171] As patients began surviving longer, the chronic toxicities of radiation became more apparent and less acceptable, and efforts to improve outcome began to focus on reducing the late effects of treatment. Contemporaneously, surgical management of the primary tumor was being assiduously promul-

gated by authors such as Pritchard, who published retrospective analyses of prechemotherapy data which were interpreted to demonstrate an improvement in survival resulting from amputation or wide resection as initial treatment.[149] Pritchard also published observations indicating that patients in IESS-I had superior time to relapse and survival when surgical resection was a component of treatment. In that study, pelvic primaries were more frequently treated nonsurgically, and multivariate analysis of survival identified pelvic primary tumor as an adverse prognostic factor.[151] Nonetheless, the nonrandomized assignment of more favorable primary tumors to surgery allowed the conclusion that surgery was at least as good as radiation in treatment of the primary site in patients with localized disease.[151]

Although randomized comparisons are lacking, local control of lesions treated with surgery alone or surgery plus radiation have been excellent. Local control rates following surgery ± radiation average 94%. The results of several surgical resection series are summarized in Table 5.14. Disease-free survival and overall survival following resection compared favorably to results obtained with radiation. Despite selection of small, noncentral, or nonpelvic tumors which would have a good prognosis regardless of the local therapy, surgical resection in some instances may be slightly effective in preventing local recurrence.[153,172] The use of lower doses of radiation following surgical resection is theoretically appealing in that late effects including second cancers might be reduced in comparison to full-dose radiotherapy.[172] However, this has not been adequately assessed in prospective studies, and the routine use of both surgery and radiotherapy has been questioned.[173]

Notwithstanding the excellent results for surgical resection alone or combined with radiation in highly selected patients, very good to excellent results have been reported for induction chemotherapy followed by local radiotherapy. Local control results obtained with radiation as the local modality range from 44% to 100%, and are affected by pretreatment factors such as primary site and tumor volume, as well as treatment-related factors such as the response to chemotherapy and radiotherapy technique. The results of radiation therapy for Ewing's sarcoma are summarized in Table 5.15.

The IESS-I and IESS-II established the standard to which the results of radiation and chemotherapy must be compared. IESS-I evaluated the additions of Adriamycin and pulmonary radiation to vincristine, actinomycin, and cyclophosphamide (VAC) chemotherapy in the multimodality treatment of non-metastatic Ewing's sarcoma. Long term results were reported for 331 patients,[171] and radiotherapy results were reported for 271 patients.[174] Relapse-free survival and overall survival at 5 years were superior when Adriamycin was added to VAC compared to VAC alone ($p < 0.001$).

This study also demonstrated that pulmonary irradiation improved relapse-free and overall survival when added to VAC, compared to VAC alone ($p < 0.001$). The results of IESS-I are summarized in Table 5.16. The difference between the group treated with Adriamycin and the group treated with pulmonary radiation was less pronounced, and reached statistical significance only when all eligible randomization groups were considered.[171] Local control for all patients was 89.2%, with no significant differences among the treatment groups.[174] Despite the lack of statistical significance, local control in patients with inadequate radiotherapy volumes or doses was improved with the addition of Adriamycin (90% versus 71.4%).[168,174] Pelvic primary site and age >15 years were associated with a poor prognosis.[171]

In IESS-II, high-dose intermittent Adriamycin was compared to lower dose continuous infusion

Table 5.14 Local control following resection ± radiation for extremity Ewing's sarcoma

Reference	*Institution*	*No. of patients*	*Local control*	*5-year survival, DFS, RFS*	*Preoperative/postoperative radiotherapy*	*Amputation*
Wilkins	Mayo	27	96% (26/27)	74%	27/27 (100%)	5/27 (18.5%)
Sauer	CESS-I	60	90% (54/60)	64%	29/60 (48%)	ND
Sailer	MGH	12	100%	92%	92%	1/12 (8%)
Hayes	St Jude	11	100%	80%*	0	ND
Arai	St Jude	17	100%	75%	7/17 (18%)	ND
Toni	Bologna	69	96%	59%	31/56 (55)	13/69 (19%)
Dunst	CESS-II	132	96%	70%	63/91 (69%)	(9%)
Tereki	Brown University	22	95%	41%	13/22 (59%)	4/22 (18%)
Villoreal	Chile	16	100%	50% (7-year)	50%	ND

*This survival estimate is for all treated patients. Only two relapses occurred among the 11 patients treated with surgery alone as the local treatment. ND = Not described; DFS = disease-free survival; RFS = relapse-free survival.

Table 5.15 Results of radiotherapy for Ewing's sarcoma

Institution	*Years*	*No. of patients*	*Chemotherapy agents*	*Radiation dose*	*Volume*	*Local control*	*5-year EFS/DFS*	*Reference*
MGH	1930–1952	22	None	2000–6000 r	WB	68%	18%	Wang *et al.*[1]
UCSF	1945–1965	20	None	16–65 Gy	WB	72%	25%	Phillips and Sheline[2]
IESS-I	1973–1978	148*	VACA	55–65 GY	WB	89%	60%*	Nesbit and Rosen[71]
IESS-II	1978–1982	108†	VACA	55 GY	WB	93%	73%†	Burgert *et al.*[175]
CESS-I	1981–1985	32	VACA	45–60 GY	WB	54%[a]	44%	Sauer *et al.*[158]
CESS-II	1986–1991	44	VACA/VAIA	60 Gy	PB	86%	70%	Dunest *et al.*[177]
St Jude	1978–1988	43	VA/CA/BCNU	30–60 Gy	PB	58%[b]	53%	Arai *et al.*[155]
NCI	1968–1980	107	VC/VAC/VADRIAC	50 Gy	WB	80%	29%	Kinsella *et al.*[163]
NCI	1986–1992	46	VADRIAC/IE	26–63 Gy	N/A	80%	42%	Wexler *et al.*[165]
Chile	1986–1991	11	VACA	45–63 Gy	PB	73%	36%	Villareall *et al.*[161]
Scandinavia	1984–1990	17	VACAMB	40–60 Gy	N/A	76%	35%	Nilbert *et al.*[181]
UK	1978–1986	108	VACA	32–55 Gy	WB	69%	35%	Craft *et al.*[184]
Bologna	1972–1987	62	VA/VACA	35–60 Gy	WB/PB	66%	N/A	Toni *et al.*[154]
University of Florida	1971–1990	31	VADRIAC	50–68 Gy	WB/PB	77–81%	N/A	Bolek *et al.*[166]
POG 8346	1983–1988	94	AC/VAC/VACA	55.8 Gy	WB/PB	65%	41%	Donaldson *et al.*[157]

*Best treatment arm of IESS-I – VAC and Adriamycin
†Best treatment arm of IESS-II – VAC and high-dose intermittent Adriamycin – 43% of patients had surgical resection
[a]90% of patients (17/19) with local relapse had violation of radiation protocol
[b]Lower doses and limited volumes were associated with reduced local control
[c]16/21 (76%) of local failures occurred in patients treated with ^{137}CS prior to chemotherapy

Gy = Gray; r = roentgen; PB = partial bone; WB = whole bone; VAC = vincristine, dactinomycin, cyclophosphamide; VACA = vincristine, dactinomycin, cyclophosphamide, Adriamycin; VA = vincristine, dactinomycin; CA = cyclophosphamide, dactinomycin; VACA = vincristine, dactinomycin; cyclophosphamide, Adriamycin; VAIA = vincristine, dactinomycin, ifosfamide, Adriamycin; VADRIAC = vincristine, Adriamycin, dactinomycin, cyclophosphamide; IE = ifosfamide, etoposide; VC = vincristine, cyclophosphamide; AC = Adriamycin, cyclophosphamide; VACAMB = vincristine, dactinomycin, cyclophosphamide, Adriamycin, methotrexate, bleomycin; BCNU = bis-chlorethylnitrosourea.

Adriamycin. All patients received four-drug chemotherapy and radiotherapy. In patients with nonpelvic primary tumors, surgical resection was encouraged by study investigators. This resulted in amputation, or resection in 43% of all patients. The radiotherapy protocol was identical to IESS-I and consisted of treatment of the entire bone to 45–55 Gy followed by a 10 Gy boost to the tumor site plus 5 cm margin. Relapse-free, disease-free and overall survival were superior with high-dose intermittent Adriamycin compared to low-dose continuous Adriamycin (73%, 68% and 77% versus 56%, 68%, and 63%, respectively; $p < 0.05$). Local control for all patients enrolled was 91%, with no significant difference in local control between the randomized groups (93% versus 90%).[175] Increasing awareness of the late toxicities of whole-bone radiotherapy led previous investigators to analyze patterns of local recurrence relative to the irradiated field. Noting that the great majority of local recurrences develop in sites identified radiographically, Suit suggested reducing the dose of radiation to uninvolved intermedullary sites when aggressive chemotherapy was to be used.[170]

Table 5.16 Results of IESS-I (percentages)

Endpoint	*Treatment 1*	*Treatment 2*	*Treatment 3*
5-year recurrence-free survival	60	24	44
5-year survival	62	23	51

Treatment 1: radiotherapy to the primary lesion plus VACA (vincristine, dactinomycin, cyclophosphamide, Adriamycin).
Treatment 2: radiotherapy to the primary lesion plus VAC (vincristine, dactinomycin, cyclophosphamide).
Treatment 3: radiotherapy to the primary lesion plus VAC (vincristine, dactinomycin, cyclophosphamide) and bilateral pulmonary radiation.

The German Co-operative Ewing's Sarcoma Study (CESS) I sought to evaluate multimodality therapy for non-metastatic Ewing's sarcoma, and to test lower-dose radiotherapy treatment of the primary site. All patients received local treatment following weeks 18–20 of chemotherapy (VAC plus Adriamycin). Radiation doses were 36 Gy following resection with positive margins,

50–60 Gy for patients with central/pelvic lesions, and extremity lesions were randomized to receive either 46 Gy or 60 Gy. Shrinking-field technique was used which consisted of 36 Gy delivered to the whole bone, followed by treatment of the tumor bed plus 5 cm margin to 45 Gy, and finally treatment of the tumor bed plus 2 cm margins to 60 Gy. In this study, assignment of local resection or radiation was nonrandomized and based on physician preference. Local control, disease-free survival and overall survival following resection was 97%, 65%, and 62%, respectively. For the resection plus radiation group, local control, disease-free survival, and survival at 5 years was 83%, 69%, and 66%, respectively. The results for the radiation-alone group were disappointing, with local control, disease-free survival, and survival at 5 years equal to 54%, 44% and 28%, respectively. The worse-than-expected results for the radiotherapy arm, which were confirmed by an interim analysis, prompted centralization of radiotherapy planning and quality assurance in 1984.[158] Although radiotherapy results improved with better radiotherapy quality assurance (i.e. there were no further local failures), a large percentage of patients had been enrolled prior to improvements in radiotherapy planning, and these patients were not excluded from analysis of the study results. Significant prognostic factors identified in that study included a good histopathologic response to chemotherapy in the resected tumor, and tumor volumes <100 ml. There was no significant difference in the relapse rates for patients randomized to low-dose or high-dose radiation.[158,176] The authors postulated that high local failure rates with radiotherapy alone resulted from: (a) late initiation of local therapy (week 18); (b) a larger percentage of central and proximal tumors in the irradiated group; and (c) protocol deviations which were noted in 17/19 patients who had local relapse following radiotherapy.[158,176]

In the subsequent CESS 86 study there were several changes in protocol design which reflected the experience gained from CESS 81. These included centralized radiotherapy planning and quality assurance, earlier implementation of radiotherapy (week 9 rather than week 18) and greater utilization of surgical resection (approximately 75% of patients).[177] The chemotherapy regimen consisted of VAC with Adriamycin as in CESS 81, alternating with VAIA (in which ifosfamide with mesna was substituted for cyclophosphamide). The nonrandom assignment of local treatment was as follows: surgical resection alone (39 patients); surgery and radiotherapy (93 patients); radiation alone (44 patients). Forty-five gray was given following resection, and 60 Gy was given when radiation alone was used for local treatment. Patients receiving radiation were randomized to conventional fractionation or a split-course hyperfractionated regimen. Local control following surgery, radiotherapy, and surgery plus radiotherapy was 100%, 86%, and 95%, respectively. No statistical comparison of local control rates for surgery versus radiation alone was provided. However, there were no statistical differences in relapse-free or overall survival between the surgery, radiation alone, or surgery plus radiation groups. No significant differences in the 5-year local control (82% versus 86%), relapse-free survival (53% versus 58%), or survival (63% versus 65%), were observed between conventional and hyperfractionated groups, respectively. Unlike CESS 81, tumor volume and response to chemotherapy were not significant prognostic factors. The improved results obtained in CESS 86 were primarily due to improved local control of the primary site. The improved local control was believed to result from: (a) earlier implementation of radiotherapy; (b) the use of higher doses of radiation in larger percentage of patients; (c) improved radiation technique with centralized planning; (d) the more frequent use of surgery; and (e) the more frequent use of combined surgery and radiotherapy for local treatment in patients with high risk features (i.e. pelvic primaries). Indeed, the most striking improvements were observed in patients with tumor volumes >100 ml, and in patients with pelvic primary tumors who the authors concluded should be treated routinely with combined local therapy.[177]

More recently, Bacci *et al*. analyzed prognostic factors in 359 patients with nonmetastatic Ewing's sarcoma. The analysis includes patients treated over a 16-year period (1979–1995) with four different Adriamycin-containing chemotherapy regimens, the most recent of which employed ifosfamide as one of the induction agents. Local therapy consisted of surgery alone, radiation alone or a combination of the two. In general, only very young patients, and select patients with easily expendable primary sites, were treated surgically in earlier years, while there was a greater emphasis on routine surgical resection in later years. Radiation was routinely given to older patients following marginal resection, when possible. Univariate analysis of the entire group revealed a superior 5-year event-free survival for surgery compared to radiation (64.7% versus 47.5%). The local recurrence following surgery alone was 6% compared to 19% for radiation alone. The local recurrence and 5-year event-free survival rates were 8.5% and 55.7%, respectively for patients treated with surgery plus radiation. These results reflect, in part, the selection of patients with less favorable prognostic factors for radiotherapy. Multivariate analysis identified age >17 years, male sex, fever, anemia, elevated LDH, tumor location other than extremity,

and the chemotherapy regimen, as independent predictors of event-free survival when all 359 patients were analyzed. A second multivariate analysis confined to the 174 resected patients identified fever, anemia, serum LDH, and histologic response to chemotherapy as independent predictors of event-free survival.[178] Prognostic factors for Ewing's sarcoma are listed in Table 5.17.

A trial of low-dose, limited-volume radiotherapy was reported by Arai and colleagues from St Jude Children's Research Hospital.[155] Sixty cases of localized Ewing's sarcoma were treated with Adriamycin-containing induction chemotherapy, and alternating vincristine/actinomycin, and cytoxan/Adriamycin maintenance for 57 weeks. Radiographic complete response to chemotherapy occurred in 29/45 (64%) and objective response was noted in 37/45 (82%) of evaluable cases. Local therapy consisted of surgery in 17 patients (complete resection prior to chemotherapy in three patients, complete resection following chemotherapy in 14 patients). Three patients with positive microscopic margins received postoperative radiation (35–41 Gy). Local control for the surgically treated groups was 100% and the 5-year event-free survival was 75%. Forty-three patients received radiation as the primary local modality. In all cases, radiation fields were limited to 3 cm beyond osseous tumor or post-chemotherapy regional soft-tissue extension. Prior to 1985, low-dose irradiation (30–36 Gy) was utilized for: (a) patients having complete response to chemotherapy, (b) patients with negative post-chemotherapy biopsies, and (c) cases with no measurable soft-tissue extension prior to chemotherapy. "High-dose" (50–60 Gy) radiotherapy was utilized for all patients with progressive disease, and those with biopsy-confirmed residual disease following chemotherapy. Following 1985, high-dose radiation therapy was used for all patients with tumors > 8 cm at diagnosis. Local control and event free-survival for the radiotherapy group was 58% and 53%, respectively at 5 years. These results were significantly inferior to the surgically resected group ($p = 0.044$). Surgically resected patients consisted of a more favorable group who had smaller, nonpelvic primary tumors. Tumor diameter and response to induction chemotherapy were significant predictors of local control and event-free survival in the radiotherapy group. In the "low-dose" group, local control of tumors < 8 cm in diameter was 90% while for tumors greater than 8 cm it was 52%. A surprisingly low 5-year local control rate of 39% was reported for the "high-dose" group, although no exploration or discussion of this aspect of the St Jude experience was offered. Although the local failure rate was high, local recurrence was central within the target volume in 18/19 (95%) of the cases. The authors concluded that the limited irradiation volume did not affect local control, that tumor size and response to chemotherapy were predictive of outcome, and that low-dose radiotherapy could *not* be routinely recommended regardless of the response to chemotherapy.[155]

Table 5.17 Prognostic factors in 359 nonmetastatic Ewing's sarcoma determined by multivariate analysis (modified from ref. 178)

Variable	P-*Value*
Age	< 0.001
Sex	< 0.04
Fever	< 0.0002
Anemia	< 0.02
LDH	< 0.0003
Tumor site	< 0.02
Chemotherapy regimen	< 0.00003
Histologic response to chemotherapy*	< 0.00001

*Results from 179 surgically resected patients analyzed in a separate multivariate analysis from entire cohort of 359 patients.

In another prospective study of radiotherapy technique, the Pediatric Oncology Group trial 8346 addressed whether "involved field" (IF) radiotherapy was as effective as "standard field" (SF) radiotherapy in the treatment of Ewing's sarcoma.[157] SF was defined as whole-bone radiation to 39.6 Gy followed by a boost to the prechemotherapy tumor volume, plus 2 cm for a total dose of 55.8 Gy. IF was defined as the tumor volume at presentation plus 2 cm. This also received a total dose of 55.8 Gy. All patients received induction chemotherapy with planned local treatment at week 14. Surgical excision was encouraged for primaries within expendable bones. A preliminary analysis in 1986 revealed a low number of patients being entered in the radiotherapy randomization due to a greater than expected number of patients presenting with either metastatic disease or small, surgically resectable localized tumors. The radiotherapy randomization was discontinued in favor of treating all patients with IF radiotherapy on study. Patients with systemic relapse underwent biopsy of the primary site if it did not appear to be involved clinically. One hundred and forty-one evaluable patients presented with localized disease. The overall response to chemotherapy was 88% and the complete response rate was 28%. Thirty-seven patients underwent surgical resection, with 16 (43%) requiring postoperative radiotherapy. The 5-year event-free survival for patients undergoing surgery was 88% and the local control for this group was 88%. The event-free survival and local control for the radio-

therapy group was 41% and 65%, respectively. Control rates differed significantly as a function of primary site. Central, pelvic/sacral, proximal, and distal extremity sites had local control rates of 82%, 44%, 69% and 80%, respectively ($p = 0.02$, log rank). There was no difference in local control for IF (53%) and SF (53%) radiotherapy. The quality of radiotherapy technique was significantly associated with local control. Patients treated without any deviation from the radiotherapy protocol enjoyed an 80% local control rate, while those with minor and major radiotherapy protocol violations had local control rates of 48% and 16%, respectively ($p = 0.005$). Analysis of the pattern of local failure revealed recurrence within the irradiation volume in 18/29 (62%) cases, and outside of the irradiated volume in 7/24 (24%). The reported chronic toxicities consisted of three second bone sarcomas, one of which arose in a nonirradiated bone, and orthopedic complications in 39% of surgically resected patients.[157] An example of "tailored field" radiotherapy for a Ewing's sarcoma of the distal femur is shown in Figure 5.9.

The above two studies, which explore reduced radiation dose and volume in the treatment of the primary site, highlight the critical importance of adequate radiotherapy technique and the attention to detail required to cure Ewing's sarcoma with radiotherapy. In the St Jude experience, local failures in the low-dose radiotherapy groups occurred within the tumor bed in 18/19 cases. While this may indicate that a "limited volume" of 3 cm margin on osseous and soft-tissue extent of tumor was an adequate volume to treat, it is quite possible that the central local failures resulting from "low-dose" (30–36 Gy) radiotherapy may have prevented detection of marginal or out-of-field failures which may have become clinically evident with more durable central control.[155] Indeed, with higher prescribed tumor doses and "tighter" margins, 24% of local failures were outside of the irradiated volume in the POG trial.[157] It should be noted that the lowest local control rates were obtained for pelvic primary sites, where tumors are typically large and doses of >60 Gy have been used with some success.[179] It is possible that the percentage of marginal recurrences may have increased with higher local doses in those patients with pelvic primary sites.[157]

From these studies it can be assumed that doses <55 Gy and radiotherapy margins <4–5 cm should not be routinely used outside of well-planned clinical trials when radiotherapy alone is to be relied upon for local cure of Ewing's sarcoma. The radiotherapy target volume should be defined only after meticulous review of MR, CT and plain-film studies with a musculoskeletal radiologist and orthopedic oncologist. With regard to postoperative radiation for close or positive margins, there are no data in the Ewing's sarcoma or radiotherapy literature which suggest that the prescribed dose of radiation can be determined by the pathologic response in the resected specimen, despite reports that the pathologic response (extent of necrosis) in the resected specimen predicts disease-free survival.[158,176,180,181]

Pelvic Ewing's

Pelvic primary tumors have been associated with a poor prognosis.[155–157,162,168,171,174,182–189] This has been attributed to a delay in diagnosis resulting in more locally advanced primary tumors with a higher propensity for metastatic relapse.[182,190] Local control of bulky pelvic Ewing's is particularly challenging, and the superiority of either surgery, radiotherapy or combined treatment remains controversial.

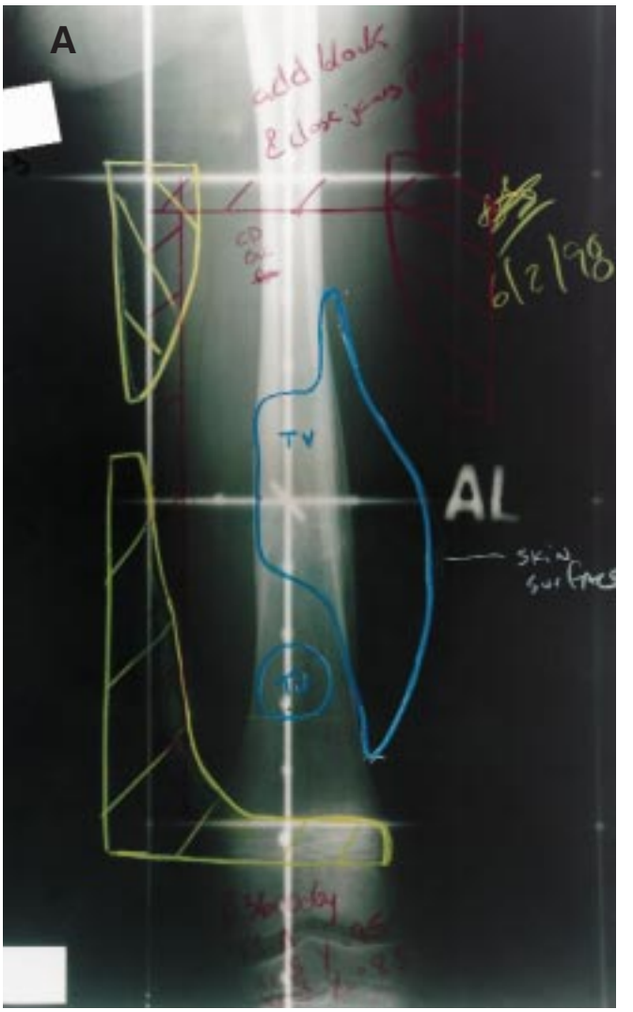


Figure 5.9 Continued on next page

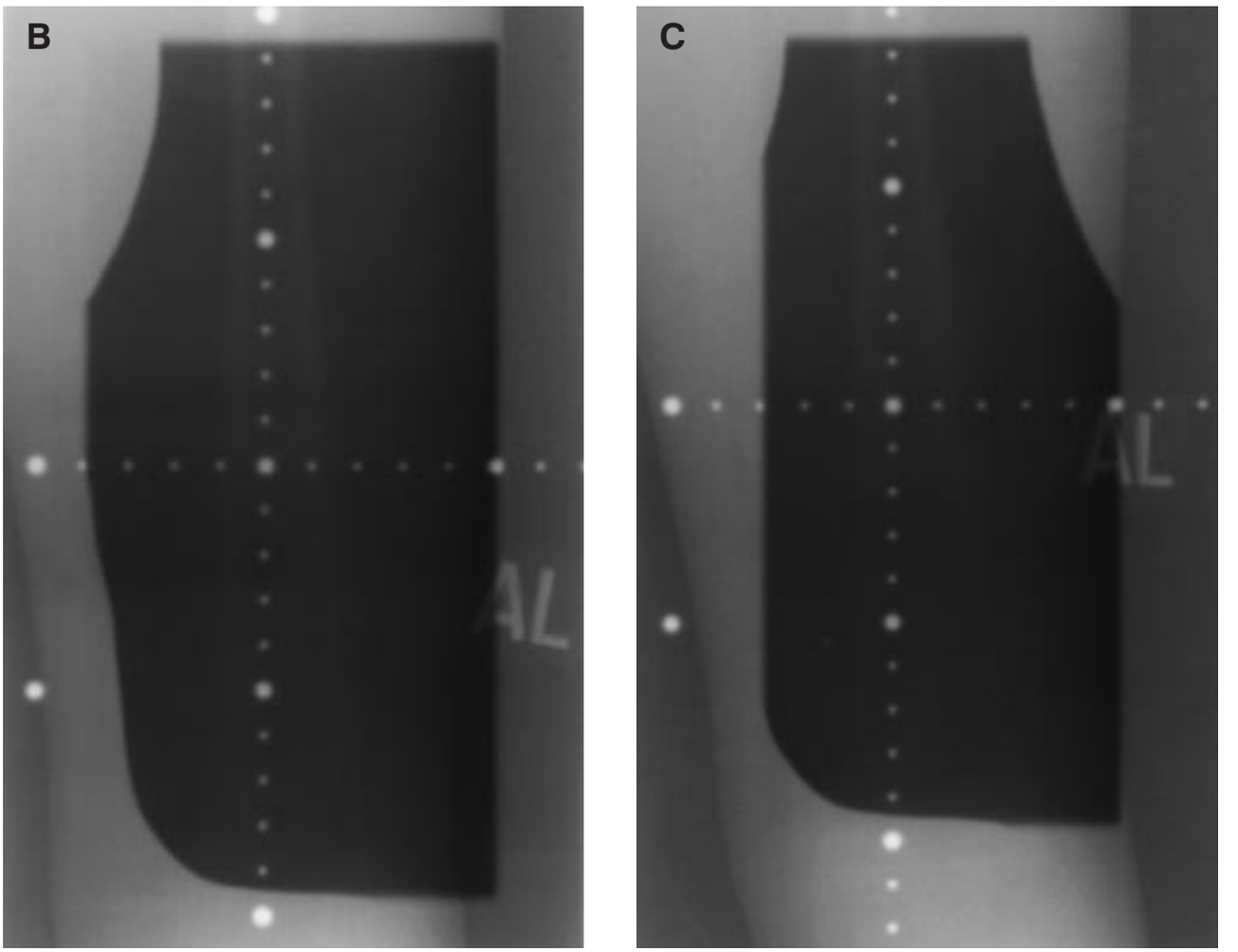


Figure 5.9 *(continued from previous page)* Tailored field radiotherapy for Ewing's sarcoma of the distal femur. The anterior simulation film is shown in (**A**). The bone and soft-tissue components of the pre-chemotherapy tumor volume (TV) are treated with 2–3 cm margin. After 3600 cGy the field is 'coned down' with additional blocks and a reduction in field size to limit the coverage to the TV plus 2 cm. A port film of the initial field is shown in (**B**), and a port film of the 'cone down' field is shown in (**C**).

IESS-I experience with Ewing's sarcoma of the pelvic bones was reported initially by Evans *et al*.[182] Sixty-two patients with non-metastatic Ewing's sarcoma of the pelvis were randomized to receive VAC, VAC plus Adriamycin, or VAC plus bilateral pulmonary irradiation. The median time to relapse for pelvic primaries on IESS-I was 92 weeks compared to 222 weeks for nonpelvic lesions ($p = 0.002$). In contrast to nonpelvic primaries, there was no difference in the rate of metastatic relapse between treatment regimens for patients with pelvic primaries. There was no relationship between local control and radiation dose (4000–6000 cGy) or field size (less than or greater than 5 cm margin). Local control was not significantly improved in the 11/62 (18%) of patients treated with complete resection (82%) compared to those treated with biopsy and radiotherapy (72%). Local control and time to relapse were decreased for all lesions 10–15 cm in diameter compared to those <5 cm. Fifty percent of pelvic lesions were 10–15 cm, in contrast to only 34% of lesions at other sites treated on IESS-I. In the long-term follow-up report of the IESS-I study, Nesbit *et al*. reported 5-year survival of 34% for pelvic sites compared to 57% for nonpelvic sites ($p < 0.01$). Similarly, there was no difference in survival by treatment regimen for pelvic primaries, in contrast to nonpelvic primaries, for which the addition of Adriamycin improved survival ($p = < 0.01$).[171]

In response to the higher rate of metastatic relapse and local recurrence in IESS-I, all patients with pelvic primaries were treated with high-dose intermittent chemotherapy containing Adriamycin and surgical resection whenever possible in IESS-II. Unlike IESS-I, CT scanning was routinely employed for radiotherapy treatment planning. The results were significantly superior to IESS-I. The local recurrence rate of pelvic primaries was 12% for IESS-II compared to 28% for IESS-I ($p = 0.03$). The rate of metastatic relapse was significantly reduced in IESS-II (37%) compared to IESS-I (67%, $p = 0.004$). The 5-year relapse-free survival and overall survival were 55% and 63% for IESS-II versus 23% and 35% for IESS I respectively ($p = 0.002$). Surgically resected patients had fewer local recurrences (1/19), than did patients treated with biopsy only and radiation (6/39). A statistical comparison of local control for resected and nonresected patients was not provided. However, there was no difference in relapse-free survival or overall survival between resected and nonresected patients. The authors concluded that the increased use of resection, along with better radiotherapy and more intense chemotherapy, achieved their goal of improving survival in patients with pelvic Ewing's sarcoma.[191]

Despite the encouraged use of resection and the improved outcome on IESS-II, the benefit of resection in patients with pelvic Ewing's sarcoma has yet to be proven in a randomized trial. Single-institution retrospective analyses from Memorial Sloan Kettering and Mayo Clinic suggest that resection improves outcome. Li *et al*. reported improved survival associated with surgical resection and contemporary chemotherapy in 10 patients, compared to eight patients treated with an earlier chemotherapy regimen and radiotherapy. Three of the 10 patients in the radiation group developed metastatic disease, compared to only one patient in the resected group. The authors admitted that the improved outcome was in part a result of improved chemotherapy. Unfortunately, the contribution of resection could not be assessed in this study due to the selection of more favorable patients in the surgery group who received more modern chemotherapy.[192]

Frassica *et al*.[193] detailed the Mayo Clinic experience with Ewing's sarcoma of the pelvis. Twenty-seven patients were reviewed, six with metastatic disease at diagnosis. Eight patients had resection with or without radiation and chemotherapy and 13 patients had chemotherapy and radiation. Four of 13 (30%) patients developed a local recurrence with or without metastatic relapse in the radiotherapy group and the actuarial local relapse rate was 44%. In the resection group, 50% underwent hemipelvectomy (three formal hemipelvectomies and one internal hemipelvectomy). Postoperative radiotherapy was used in 50% of resected patients. Local recurrence and death from metastatic disease occurred in one patient following hemipelvectomy, and metastatic recurrence developed in one patient who received an internal, then formal, hemipelvectomy. The actuarial 3- and 5-year survival rates were both 75%, and the actuarial local control rate was 88% for the resected lesions. Although resected patients did better, selection bias and treatment differences prevent any conclusions regarding the superiority or resection in that study.[193]

A series of 39 patients with pelvic Ewing's sarcoma from Boston Children's Hospital and the Massachusetts General Hospital was reported by Scully and colleagues.[189] All patients were treated with various chemotherapy regimens used throughout the study period of 1975–1991. Local treatment consisted of radiation alone in 20 patients, surgery alone in three patients and resection plus radiation in 16 patients. All surgically treated patients (19) were compared to those treated with radiation-alone (20) patients. Twelve patients presented with metastatic disease; eight received radiation alone and four were treated with surgery ± radiation. Local failure occurred in six patients; three following resection (local control = 16/19, 84%) and three following radiation (local control = 17/20, 85%), with no difference between the two groups ($p = 0.96$). Patients with metastatic disease at presentation had shorter median survival (25 months versus 44 months, $p = 0.013$). There was a trend for longer relapse-free survival in resected patients (22 months) compared to those treated locally with radiation alone (16 months, $p = 0.336$). Similarly, there was a longer median survival for the resected group (42 months) compared to the radiation group (25 months), although this difference was nonsignificant ($p = 0.13$). The overall survival for all 39 patients was only 38%, perhaps reflecting the influence of metastatic disease at presentation in 30% of the study cohort. The authors concluded that a resection was not associated with a significant disease-free advantage despite the inherent bias favoring the resected group. Indeed, the percentage of patients with metastases at presentation in the radiation group was twice that of the resected group (40% versus 20%), and a subgroup analysis excluding metastatic patients was not provided. Notwithstanding, the local control rates were virtually identical for resected and irradiated groups.[189] A lack of significant difference in outcome between irradiated and resected patients with pelvic primaries was also reported by Evans for IESS-II patients, and by Bacci *et al*.[188,191]

The available data justify the use of resection of pelvic sites when functional morbidity and disfigurement will

be minimal or non-existent. In doing so, surgical resection of the primary site augments local control, and reduces the patient's risk of suffering a radiation-induced bone sarcoma at the primary site. However, with appropriately aggressive chemotherapy and well-planned radiation, local control rates exceed 80%, and the risk of second cancer at 15–20 years equals 3–7%.[194,195] Since systemic relapse is at least 3 times as likely as local failure in patients with pelvic Ewing's sarcoma, advances in systemic treatment of this disease will have greater impact on survival than improvements in local therapy. However, given the ominous prognosis of local failure, optimization of local therapy remains the second most important goal in the management of pelvic Ewing's sarcoma. A randomized trial, as proposed by Horowitz *et al*.,[196] is needed to prove any incremental improvement of disease-free or overall survival afforded by resection.

Radiation-induced Sarcoma Following Treatment of Ewing's Sarcoma

Ewing's sarcoma patients appear to be at an increased risk for radiation-associated bone and soft-tissue sarcomas in comparison to other solid tumors of childhood – their risk being second only to children with bilateral retinoblastoma.[194,197] Although the reported cumulative incidence of radiation-induced sarcoma varies from 5.5% to >35% at 20 years,[195,197–199] there is agreement among reports that the risk of a radiation-induced sarcoma increases with time and radiation dose.[195,197,199] In an early report from the late-effects group, Tucker *et al*. reported a 20-year incidence of 22.1% for patients who received radiotherapy for Ewing's sarcoma. Their analysis revealed that doses >60 Gy, and increasing exposure to alkylating agents, significantly potentiate the risk of radiogenic bone sarcoma.[197]

Kuttesh and colleagues from the NCI, St Judes and the University of Florida at Gainesville reviewed 266 survivors of Ewing's sarcoma, all of whom had received radiation with or without chemotherapy. Sixteen patients developed a second malignancy with a median latency period of 7.6 years. Ten of the 16 malignancies were sarcoma (five osteosarcoma, three fibrosarcomas, and two malignant fibrous histiocytomas). All second solid malignancies occurred at the primary site or within the irradiated volume. The median radiation dose received in the ten patients was 61.1 Gy (range 50–64 Gy). The remaining six neoplasms included acute lymphoblastic leukemia, acute myeloblastic leukemia, meningioma, basal cell carcinoma, bronchoalveolar carcinoma and carcinoma-*in-situ* of the cervix. The patients who developed meningioma, basal cell carcinoma and bronchoalveolar carcinoma had received local radiotherapy to the sites of the second neoplasm, or had received total-body irradiation (bronchoalveolar carcinoma). The cumulative incidence of a second neoplasm was 5% and 9.2% at 10 and 20 years postdiagnosis, respectively. For secondary sarcoma the cumulative estimated incidence rates were 3% and 6.5% at 5 and 10 years postdiagnosis. A dose–response relationship was reported for the risk of secondary sarcoma. The absolute risk of secondary sarcoma was zero for patients who received <47.99 Gy, 24.9 cases per 10,000 person-years for doses between 48–59.9 Gy, and 131 cases per 10,000 person-years for those receiving doses ≥ 60 Gy. These are approximately equivalent to 5% at 20 years for doses between 48 and 59.9 Gy, and 21% at 20 years for doses ≥ 60 Gy. In this pooled data set more secondary sarcomas occurred in patients treated at the NCI where higher doses were used more routinely.[200]

The risk of osteosarcoma in 4257 survivors of childhood cancers in France and Great Britain who presented with tumors other than osteosarcoma was recently analyzed by Le Vu and colleagues. The 20-year cumulative incidence of second osteosarcoma was 6.7% following treatment of Ewing's sarcoma. The risk of osteosarcoma was radiation dose-dependent, and the relative risk per unit dose was lower among Ewing's sarcoma patients, suggesting the possibility that genetic predisposition may contribute to the development of second osteosarcomas in patients with primary Ewing's sarcoma.[194]

Finally, Dunst *et al*. recently reviewed the CESS 81 and CESS 86 database for second malignancies following treatment of Ewing's sarcoma. Eight second malignancies were reported in a cohort of 640 patients. There were four leukemias, one myelodyplastic syndrome, one osteosarcoma, one fibrosarcoma, and one malignant fibrous histiocytoma. All three second solid malignancies occurred in irradiated patients and were located partially or completely within irradiation volume. The risk of developing any second malignancy was 4.7% at 15 years, and the risk of a second solid malignancy was between 3% and 6% following radiotherapy at 15 years. Three out of five patients with leukemia died of rapid progression. In contrast, two out of three patients with second solid malignancies were salvaged with surgery and chemotherapy, and are alive without disease 4.3 and 7.5 years following diagnosis.[195] Despite reports of second sarcomas developing in >35% of survivors at 20 years,[199] the risk of a radiation-induced second sarcoma in more contemporary cohorts of Ewing's survivors is between 3% and 7% at 20 years when doses below 60 Gy are used.[194,195,200,201] Since the risk of second sarcoma is time- and radiation dose-dependent, additional follow-up is needed to more

adequately assess the incidence of second sarcoma in modern cohorts. Existing data suggest that the risk of second cancer increases significantly when doses >60 Gy are used.

OSTEOSARCOMA

Extremity

The past 30 years have witnessed dramatic improvements in the treatment and survival of patients with osteosarcoma. Multiagent chemotherapy regimens which include high-dose methotrexate, doxirubicin, cisplatin, and ifosfamide have been shown in single-institution[202–207] and cooperative trials[208,209] to significantly prolong survival. Chemotherapy has also demonstrated its ability to sterilize tumor at the primary site. This finding, which is of prognostic importance,[202,210] provides an intuitive reassurance regarding limb-salvage surgery, as well as information which can be used to optimize adjuvant chemotherapy.[211] The ability of chemotherapy to improve local control, combined with the dramatic improvements in surgical techniques and prosthetics, has allowed limb- and/or function-sparing surgery following neoadjuvant chemotherapy to be offered to the majority of patients with improved results.[203,212] The role of radiotherapy in the routine management of extremity osteosarcoma is virtually nonexistent today. However, radiotherapy has been reported to improve local control of borderline or unresectable extremity osteosarcoma, vertebral osteosarcoma and pelvic osteosarcoma.[66,70,73,74,121,213,214] It has also been used to successfully treat osteosarcomas of the mandible.[215–218] Due to space limitations, treatment of craniofacial osteosarcoma with radiation will not be discussed, and the reader is referred to an excellent recent review.[219] High-LET radiotherapy, preoperative radiotherapy and radiation sensitizers have been used successfully for treatment of osteosarcoma.[72,121,220,221]

Radiotherapy was originally proposed by Ferguson[222] and again by Cade[223] in the 1950s as means of local treatment which might alleviate symptoms and delay amputation in the patient presenting with localized disease, so as to allow occult metastases to declare themselves, thus enabling the avoidance of a non-curative amputation. Radiation doses of 70–90 Gy were delivered in 8–12 weeks followed in 6–9 months by amputation.[223]

This strategy was implemented in 23 patients reported by Phillips and colleagues at the University of California San Francisco. Treatment consisted of preoperative radiation (50–100 Gy) and amputation. When compared to 11 patients treated with amputation alone there was no significant difference in survival. In six cases no viable tumor was seen at amputation, and all but one of the six had received 100 Gy.[2] Allen and Stevens compared preoperative radiation (79–100 Gy) in 10 patients to 20 patients treated with surgery alone, and claimed a survival advantage at 5 years (60% versus 10%) in favor of preoperative radiation.[224] In an early Princess Margaret experience, preoperative radiation was administered to 29 patients, 27 of whom were evaluable. No patients received >80 Gy, and three patients were treated under conditions of hypoxia. All 27 evaluable patients locally recurred after a mean duration of only 3.6 months. The authors concluded that preoperative irradiation failed to provide durable palliation, did not allow identification of those who could be spared amputation, nor did it prolong survival.[225] In addition, single- and multiple-institution studies[226–229] demonstrated improved response rates and superior disease-free survival with the use of chemotherapy, allowing many to conclude that delaying surgical resection (and postoperative chemotherapy) in order to administer radiotherapy was contraindicated. The substantial responses to chemotherapy, and the delay in resection required to construct an orthopedic prosthesis, led Rosen and colleagues to advocate preoperative, or neoadjuvant, chemotherapy[202,211]. Local control with this approach in the current era of en-bloc resection and limb-salvage procedures has been excellent.[70,202,203,230]

Preoperative radiation combined with intra-arterial infusions of radiation sensitizers or chemotherapy agents has described by several investigators.[66,70,73,121,230–233] This treatment strategy has been described by Eilber *et al*. in a series of reports.[66,70,230] In their initial reports Adriamycin 30 mg/day was infused over 24 h on three consecutive days followed by 3500 cGy given in 10 fractions of 350 cGy. This was followed by limb-sparing resection 7–14 days later. There were only two local recurrences in the 83 skeletal sarcomas which included 57 high-grade intermedullary osteosarcomas. Complications observed in Bone sarcoma patients were frequent and usually resulted from failure of the cadaver allografts used for limb reconstruction.[66,70]

Wiley *et al*. treated two cases of extremity osteosarcoma with preoperative intra-arterial Adriamycin and radiotherapy to 70 Gy and 80 Gy, respectively. Resection, which was performed out of concern over progressive calcification within the treated lesion, revealed extensive necrosis. However, both of these patients died of pulmonary metastases.[231] Enton *et al*. treated nine patients with osteosarcoma using preoperative treatment similar to the UCLA regimen. Intra-arterial Adriamycin was infused over 3–5 days followed by 300 cGy given in ten fractions. Limb-sparing resection was performed 7–14 days later.

Pathologic analysis revealed varying degrees of necrosis with varying degrees of viable tumor present in all specimens. There were no recurrences of osteosarcoma although follow-up was limited (9–24 months, median 16 months).[232] Goodnight and colleagues treated six patients with osteosarcoma using the UCLA regimen. All were locally controlled. Two patients with bone sarcomas required amputation as a result of wound-healing complications. The overall complication rate was 38–41%.[73] Similar results were reported by Wanebo *et al*.[74]

The intra-arterial delivery of the radiation sensitizer bromodeoxyuridine (BUDR) followed by hypofractionated radiation for osteosarcoma was reported by Martinez and colleagues at Stanford. Nine patients with unresectable primary tumors received intra-arterial infusion of BUDR, 48 h prior to 600 cGy. Treatment was given every 5 days to a total dose of 42–48 Gy. All patients also received multiagent chemotherapy every 3 weeks starting with initiation of treatment. Local control was achieved in 7/9 (78%) patients. Metastatic disease developed in 5/9 (55%) patients. Five of nine patients (55%) developed severe postirradiation fibrosis, requiring amputation in two patients. There was no viable tumor identified at pathologic analysis in the two cases treated with amputation.[121] Lejeune *et al*. treated 11 osteosarcoma patients with the Stanford regimen of intra-arterial BUDR and hypofractionated radiotherapy. Ten were evaluable for response. Local control was achieved in 9/10 cases. However, severe fibrosis developed in 83% of cases, and 6/9 patients (67%) developed severe fibrosis of the knee resulting in permanent flexion.[233]

Pelvic Osteosarcoma

Pelvic osteosarcomas are rare, constituting approximately 10% of all osteosarcomas.[234] The prognosis of pelvic osteosarcomas is often poor due to their large size at diagnosis. Involvement of joints, extension to other bones, microscopic invasion of normal muscle or pelvic organs, and extension into lymphatics and major pelvic veins are frequent findings.[214] In the University of Florida experience of 25 patients, 20 had primary tumors >10 cm and over half were >15 cm. Surgical resection was attempted in 18 patients. Of the 10 patients who underwent hemipelvectomy, in only two were widely negative margins obtained, and of the eight patients who had a limb-salvage procedure, in only two were histologically negative margins achieved. In 14 of the 18 operated patients margins were either wide and contaminated, marginal, or intralesional. Twelve of the involved margins resulted from extension of tumor to multiple adjacent pelvic bones or vertebral bodies. Intralumenal venous extensions of tumor were documented in nine operated cases. Of the five patients who survived >5 years, all received postoperative local radiotherapy, and two remained locally controlled. Only one patient out of the series of 25 was a long-term survivor. The authors recommend the use of adjuvant chemotherapy and local radiotherapy despite the fact that neither has been *proven* to increase survival for patients with pelvic primary tumors.[214]

Estrada-Aguilar and colleagues treated five patients with osteosarcoma of the pelvis (three primary, two metastatic recurrent) using intra-arterial cisplatin and radiation. Local control was achieved in all five patients, with two surviving 56 and 77 months, respectively.[235] Hoekstra and colleagues treated five pelvic osteosarcoma patients with hemipelvectomy and IORT (20–30 Gy). Four out of five were locally controlled and two of five (40%) were long-term survivors. Complications due to IORT were limited to coccygeal necrosis in one out of five patients. Local control was superior when compared to surgery alone in a group of six historical controls.[236,237] Finally, four patients with pelvic osteosarcoma were treated with neoadjuvant chemotherapy, photon radiation and a neutron boost at the Center Leon Berard and the Orleans Neutron Therapy unit in France. With a median follow-up of 24 months (range 22–40 months) all are alive without local recurrence or metastatic disease. Low patient numbers and short follow-up prevent conclusive observations. However, the results to date are promising.[238] In summary, the frequent close or positive margins resulting in high local relapse rates following surgery and chemotherapy, and the apparent benefit of adjuvant radiotherapy[235–238,240,242,243] indicate that innovative local treatments such as IORT, brachytherapy, intensity modulated radiotherapy (IMRT) or charged-particle therapy deserve further evaluation in these difficult tumors. While not proven, the role of adjuvant radiotherapy for pelvic osteosarcoma is supported by the literature.

Palliation

Radiotherapy can be utilized for palliation of metastatic osteosarcoma, and as an adjuvant to surgical resection at sites where wide margins are difficult to achieve. A consistent dose and fractionation regimen which is effective in palliating pain from primary and metastatic osteosarcoma is not readily apparent in the literature. Ten patients with osteosarcoma of the extremities received 10,000 cGy preoperatively at the University of Oregon. Seven of eight patients had successful palliation of pain in response to radiation.[224] Rosen and Martinez, at Memorial Sloan Kettering Hospital, treated

patients with metastatic osteosarcoma with combination therapy consisting of high-dose methotrexate, Adriamycin, cyclophosphamide and radiation. Radiotherapy was usually given in three high-dose fractions (400–800 cGy) in 1 week followed by 2000 cGy in 10 fractions. Six of seven treated lesions responded completely. Two patients with spinal cord compression from osteosarcoma responded to chemotherapy and four or five fractions of 400 cGy, followed by four fractions of 200 cGy. While the relative contributions of chemotherapy and radiation to the observed responses are not clear, this experience establishes a precedent for hypofractionation in the palliative treatment of metastatic osteosarcoma.[241]

Vertebral osteosarcoma has been associated with a poor prognosis even following resection and radiotherapy. Although treatment results have improved with chemotherapy, local recurrence is the major cause of treatment failure. Sundaresan and colleagues reviewed 24 patients with osteosarcoma of the spine treated at Memorial Sloan Kettering Cancer Center. Thirteen patients underwent limited resection and postoperative radiotherapy (30–45 Gy), and 11 patients treated more recently received neoadjuvant chemotherapy, complete gross excision and postoperative radiotherapy. Nine of 11 "recent" patients received radiotherapy, two of whom were treated with particle-beam therapy to doses of 70 cobalt Gray equivalents. There were no long-term survivors in the early cohort of 13 patients, while there were three patients who survived >5 years, two without disease. Of the five "long-term" survivors (36–66 months), all had received local radiotherapy. The authors recommended external-beam radiation (combined photon and particle-beam) to improve local control.[213]

Neutrons and Charged Particles

Charged-particle (protons, neon) and neutron irradiation have been evaluated as local therapy for osteosarcoma.[244–249] Lindstadt *et al*. reviewed 19 patients treated at UCSF/Lawrence Berkeley Laboratory with neon ion radiotherapy for bone sarcoma. Three out of four patients with macroscopic osteosarcoma were locally controlled. The 5-year actuarial local control for all patients with macroscopic bone sarcoma was 59%.[244,245] Proton-beam radiotherapy alone, or combined with conventional photon therapy, was utilized to treat difficult paraspinal osteosarcomas at the Massachusetts General Hospital. Eleven out of 15 patients (73%) were locally controlled. All patients except one also received chemotherapy, and seven out of 15 had died at the time of the report, for a 5-year survival of 44%, which decreased to approximately 20% at 6 years due to intercurrent and metastatic disease.[116]

Early reports of the results of neutron radiation for osteosarcoma were poor, with only one out of nine (11%) locally controlled at the Medical Research Council Cyclotron in Edinburgh[246] and only two out of nine (22%) locally controlled at Fermilab.[247] Laramore and co-workers, who later summarized the results of neutron radiotherapy for osteosarcoma for six neutron facilities in the US and overseas, reported an average local control rate of 55% (40/73).[248,249] Similar results were reported from Germany[250] and from a review of the world experience by Wambersie *et al*., in which 54% (52/97) were locally controlled.[251] With the development of less expensive, and more practical, hospital-based neutron and charged-particle capabilities, treatment of unresectable osteosarcoma with high-LET radiation will be increasingly offered to patients as a component of combined-modality regimens.

Pulmonary Irradiation

The lungs are the most frequent site of osteosarcoma relapse (90%) with or without adjuvant chemotherapy.[252] Experience with adjuvant pulmonary radiation has been conflicting and, for the most part, negative. Newton and Barrett delivered prophylactic pulmonary irradiation (1950 cGy) to 14 patients who were also treated with 6000 cGy radiation to the primary lesion. Patients who remained free of pulmonary metastases underwent amputation 6–9 months later. Six of the 14 patients were alive at > 4 years. The outcomes of these patients appeared superior to 14 historic controls treated by Cade without pulmonary irradiation.[253] However, a randomized trial from the Mayo Clinic published 2 years earlier found no difference in time to development of pulmonary metastases or survival between the group assigned to receive 1500 cGy prophylactic lung irradiation and local treatment, or local treatment alone.[254]

The EROTC O2 study randomized 86 patients to receive 17.5 Gy adjuvant radiation to both lungs following radical treatment of the primary tumor. The group treated with lung irradiation had a superior metastasis-free survival (43% versus 28%, p-value = 0.06). For patients under 17 years of age the difference in metastasis-free survival was significant (48% versus 28%, $p = 0.028$ with a one-tailed test of significance). There was no significant difference in survival when all randomized patients were compared at 5 years (55% with lung irradiation versus 40% without, $p = 018$).[255,256] A subsequent three-arm randomized EROTC trial comparing lung irradiation, chemotherapy, and combined lung irradiation plus chemotherapy, was reported by Burgers *et al*. in 1988. Overall survival for all patients on study was 43% at 4 years. A comparison

of the treatment arms revealed no significant difference in disease-free, metastasis-free or overall survival. The authors concluded that bilateral lung irradiation and adjuvant chemotherapy had an equal, albeit limited, benefit in patients with extremity osteosarcoma, although pulmonary irradiation was less toxic.[257] The modest 4-year disease-free survival of 28% achieved for all patients on study is clearly inferior to that reported by other investigators.[202,203,212] This fact, combined with the possibility of radiation-induced second cancers, has dulled interest in adjuvant pulmonary irradiation of osteosarcoma. There continues to be interest in adjuvant pulmonary irradiation among investigators of Ewing's sarcoma who earlier[171] and more recently have shown that it prolongs disease-free survival.[258]

CHONDROSARCOMA

Chondrosarcomas have been treated successfully by a variety of radiotherapy techniques.[108,220,239,259–264] The Princess Margaret experience with megavoltage X-ray therapy for 31 patients with chondrosarcoma was reported by Harwood *et al*. The cohort of patients treated between 1958 and 1976 was believed to represent a relatively poor prognosis group, with 11 out 31 (35.5%) arising in the pelvis, and 12/31 (39%) having poorly or de-differentiated histology. Six of 12 (50%) patients with well, moderately or unknown differentiation treated with curative intent were locally controlled for 3.5–16 years. This is in contrast to the two out of eight (25%) patients with poorly differentiated, or de-differentiated lesions who were locally controlled following radical radiotherapy (35–82.50 Gy, average dose 51 Gy). The authors concluded the following: (a) chondrosarcoma of bone is not radioresistant; (b) gross residual tumor can be permanently locally controlled with radiotherapy; (c) doses ≥ 50 Gy are needed to control chondrosarcoma; and (d) de-differentiated and undifferentiated chondrosarcomas have a distinctive natural history, with the majority of affected patients dying of metastatic disease. They recommended radical radiotherapy for unresectable tumors, for gross microscopic residual disease following resection, and for recurrent tumors following local excision.[259]

McManey and colleagues reviewed 20 patients with chondrosarcoma treated at MD Anderson Hospital with megavoltage photons and/or neutrons. Tumors arose in the pelvis in 13 patients, vertebral body in four, distal femur in two and maxillary antrum in one. Five of 11 (45%) patients treated with radiotherapy alone were alive without progression of local disease at 12–87 months (median 30 months). The overall survival for this group of patients was 54% at 30 months. Two of three patients who received postoperative radiotherapy were alive without recurrence at 44–52 months, and two of three patients treated primarily with chemotherapy and radiotherapy were without evidence of progressive disease at 15 and 29 months. Two of three patients treated with radiotherapy for recurrence following excision were without evidence of progressive disease at 19 and 77 months. In total 11 out of 20 (55%) of patients treated with curative intent who received photons and/or neutron irradiation with or without chemotherapy were locally controlled with a median follow-up of 30 months. Overall survival for the group was 65% (13 out of 20). In those patients treated primarily with radiotherapy, all four patients treated with combined photons and neutrons were locally controlled compared to only 1/7 patients treated with photons alone. The authors concluded that additional patients and longer follow-up is needed, since local persistence or recurrence of tumor was noted at times ranging from 26 to 156 months.[260] In a review of the world experience, Schmitt and Wambesie reported "persisting" local control of 56% (23 out of 41) for chondrosarcoma following fast neutron radiotherapy.[261]

Investigators from the Lawrence Berkeley Laboratory and UCSF reported the results of charged-particle (helium or neon) irradiation for 24 patients with chondrosarcoma or chordoma at paraspinal sites. Nineteen had gross subtotal resection, two had gross complete resection, and three had biopsy only. Chondrosarcomas received a mean dose of 65 Gray-equivalent (GyE), and chordomas received a mean dose of 72 GyE. The projected 3-year actuarial local control for the chondrosarcoma was 83%, and the 3-year survival was 69%. For the combined group of chordomas and chondrosarcomas 13 out of 24 patients failed locally. Previous recurrence, length of overall treatment, and larger tumor volumes were associated with higher rate of local failure.[245]

In the Massachusetts General Hospital experience with proton therapy for low-grade chondrosarcoma and chordoma of the skull base, 61 out of 68 (90%) were locally controlled. The 5-year actuarial disease-free survival was 76%. It was concluded that locally aggressive tumors adjacent to critical structures could be treated more effectively with protons which have a very sharp dose gradient, allowing higher radiation doses to lesions adjacent to critical structures.[262,263] A more recent update of the Massachusetts General Hospital proton experience with "challenging" chondroid tumors of the axial skeleton (excluding tumors for the cervical spine or base of the skull) was reported by Hug and colleagues. Six patients with chondrosarcoma were treated with doses ranging from 70.2 to 77.9 cGyE.

Four patients received radiation postoperatively, and two patients were treated with gross residual disease. The 5-year local recurrence-free survival for chondrosarcomas in this series was 100%.[116] In summary, the literature clearly indicates that radiotherapy is beneficial in the treatment of locally recurrent, unresectable or incompletely resected chondrosarcoma. These tumors should no longer be considered "radioresistant".

CHORDOMA

Chordomas are rare tumors involving the sacrum (55%), base of skull (35%) and axial skeleton (15%). They are believed to arise from remnants of the notochord.[264] They are renowned for their relentless ability to recur locally. Radiotherapy has been used to palliate symptoms, to improve local control postoperatively, and for primary treatment of unresectable or locally recurrent tumor.[264–270] Metastases from chordoma usually occur late in the course of disease, and may occur more frequently with vertebral primaries.[264]

Radiotherapy of chordoma has never been shown to benefit survival in a prospective study. Retrospective series suggest that radiotherapy is effective in palliation of local symptoms and may delay the time to local failure. Reddy *et al.* at the University of Kansas described 10 patients with chordoma. Eight out of 10 were treated with biopsy or resection and radiotherapy, and two were treated with surgery alone. Both of the patients treated with surgery alone failed locally, compared to 4/8 patients treated with radiotherapy. Six of 10 patients died of recurrent disease: five out of six with local recurrence, and one patient died of distant metastasis. The average time to recurrence following surgery and radiation was 4 years compared to 2.5 years following surgery alone. The 5-year disease-free survival was 33%.[265]

Saxton reported results for 11 patients with chordomas treated at MD Anderson. All four patients who received surgery alone suffered local persistence or recurrent tumor. Six patients were treated with radiotherapy alone and all recurred locally, although the time to recurrence was longer than in the surgery-alone group. Three of nine patients who received surgery and postoperative radiotherapy were without recurrence at 36, 72 and 80 months. The authors noted that neither surgery nor radiotherapy alone was locally curative. They suggested long-term follow-up was needed to adequately determine the success of treatment due to the risk of late local and distant relapse.[266]

The Princess Margaret experience with megavoltage radiotherapy for chordomas was reported by Cummings *et al.* Twenty-four patients were referred for radiotherapy between 1958 and 1974. The majority of patients were treated with cobalt teletherapy, and the number of patients treated prior to the availability of CT treatment planning is not disclosed. A variety of radiotherapy doses and fractionation schemes were used. There were no differences in survival based on sex, location (i.e. cervical versus sacrococcygeal) or extent of surgical resection. All patients who presented with pain as the major symptom experienced relief following irradiation, with a median duration of pain relief equaling 3.5 years. Eight patients received a second course of palliative radiation to previously treated primary sites. Six of the eight patients experienced improvement or stabilization of symptoms. Overall, a total of seven patients out of 24 were without "active chordoma" at last follow-up. The authors concluded that moderate radiation doses (40–55 Gy) are sufficient to produce symptomatic relief when conventional fractionation is used.[267]

In a series of 21 patients treated at the Malinkrodt Institute from 1949 to 1986, surgery with or without radiation was associated with a survival advantage compared to radiation alone for patients with chordoma. Surgery plus radiation produced longer disease-free survival compared to surgery alone for lumbosacral chordoma (5-year: 60% versus 28%). However, all patients treated with postoperative radiation had developed local recurrences by 10 years. The authors concluded that postoperative radiation improved disease-free survival in patients with lumbosacral chordoma.[268]

The UCSF Lawrence Berkeley experience with charged-particle radiotherapy for chordoma was initially reported by Saunders *et al.*, and more recently by Schoenthaler *et al.*[269,270] Fourteen patients with sacral chordomas were treated with neon or helium ion beam radiation at the Lawrence Berkeley laboratory. They received a median dose of 74.65 cGyE. The overall 5-year local control was 55%, with a mean follow-up of 65 months (range 22–164 months). Total resection, use of neon versus helium beams, and the absence of treatment breaks were associated with improved local control. Pain relief was achieved in all patients.[270] More recently, Hug *et al.* published results of treatment for chordomas of the sacrum and spine (excluding base of skull) in 14 patients using combined photon and proton radiotherapy. Doses ranged between 67.1 and 82.0 cGyE (mean 74.6 cGyE). Nine of 14 (64%) were locally controlled. Local control was better for primary (90%) versus recurrent (50%) chordoma. There was a trend for improved local control for doses greater than 77 cGyE.[116] Although chordomas are rare, several guidelines emerge from the literature. Chordomas are best treated with as complete a surgical resection as possible. Postoperative radiation can delay recurrence,

and it can palliate symptoms from unresectable disease. Palliation of pain can be obtained with doses of 40–50 Gy. Higher doses probably do not benefit patients with unresectable disease. However, in the postoperative setting, higher doses can be given safely with careful immobilization, MR/CT three-dimensional treatment planning and precision radiotherapy technique such as charged-particle, stereotaxic or intensity-modulated radiotherapy. Higher doses (>70 Gy) will maximize the durability of local control in the setting of a maximally resected tumor.

TREATMENT TECHNIQUES

Treatment Conference

Optimal radiotherapy for most soft-tissue sarcomas is a multidisciplinary effort requiring close cooperation between the surgeon, radiation oncologist, radiologist, pathologist, physical therapist and medical oncologist. A multidisciplinary treatment planning conference facilitates review of individual evaluation by each specialist, allows focused attention to specific details of the case (i.e. tumor histology, location, extent, operative findings, margin status) and allows the formulation of a consensus plan which addresses the medical, functional, cosmetic and psychosocial needs of the patient.

Radiotherapy Planning

Radiation Therapy Pre-Planning

An intimate knowledge of the anatomic structures involved by tumor is required to adequately plan the extent and configuration of the preoperative radiation target volume. Careful physical examination, and review of the tumor extent as depicted on staging radiographic studies with the soft-tissue radiologist and oncologic surgeon are required. Soft-tissue sarcomas usually remain confined to the muscular compartment or potential space of origin until they are very advanced, at which time multiple muscle compartment and/or anatomic structures (i.e. nerve, vessels, bone, visceral organs) can be involved. The original gross tumor volume (GTV) should be defined and carefully recorded for future comparison to treatment planning MR or CT scans.

Patient Positioning and Immobilization

One of the most critical steps in treatment planning is patient positioning and immobilization. This is done on the simulator table at the time of the initial set-up. The patient must be lying or seated comfortably to allow daily, reproducible immobilization which is as effortless as possible. The lesion should be positioned such that the entrance and exit of the beam(s) do not expose contralateral limbs or other tissues unnecessarily. Once the treatment position has been chosen, immobilization devices such as plastic casts, foam vacuum casts, or thermoplastic molds are constructed to immobilize the region to be treated. Following this, the proximal and distal borders of the region of interest are demarcated on the patient and on orthogonal plain X-rays as a set-up reference. A treatment planning CT scan, and preferably a treatment planning MR, are obtained of the demarcated area immobilized in the treatment position. CT/MR image fusion is currently employed routinely at the National Cancer Institute for radiation treatment planning of soft-tissue sarcoma. An example of a CT/MR image fusion used to plan treatment of a pelvic Ewing's sarcoma is shown in Figure 5.10.

Computer-assisted Treatment Planning

Many contemporary computer three-dimensional treatment planning systems allow CT/MR image fusion. This can be quite useful in ensuring accurate inclusion of areas of marrow involvement, and subtle periosteal/soft-tissue edema resulting from tumor infiltration, within the target volume. The tumor is outlined or contoured on a slice-by-slice basis. Once this is complete, the gross tumor volume (GTV) has been defined. With the addition of appropriate margins (see below in preoperative/postoperative volumes), this volume becomes the clinical target volume (CTV). Sarcomas tend to be irregular tapering volumes within sloping body contours. Simple AP-PA fields are rarely optimal. Multiple matched coplanar oblique fields are often necessary to produce homogeneous doses in anatomic regions which taper in thickness and depth. Wedges, compensators, electron beams and carefully planned supplemental fields should be used to avoid areas of low or excess dosages. Shaped cerrobend blocks are being replaced by multileaf collimators which also allow the use of intensity-modulation techniques. An example of the technique used to treat a soft-tissue sarcoma of the posterior thigh is shown in Figure 5.11.

Pre-operative Treatment Volume

Although it has been known for some time that sarcomas can extend along tissue planes for many centimeters,[56] and can recur more than several centimeters away from the tumor bed following resection and postoperative radiation, the required margin around the tumor has not been adequately studied prospectively in the preoperative setting. Radiotherapy volumes which treat <5 cm of normal tissue in the longitudinal

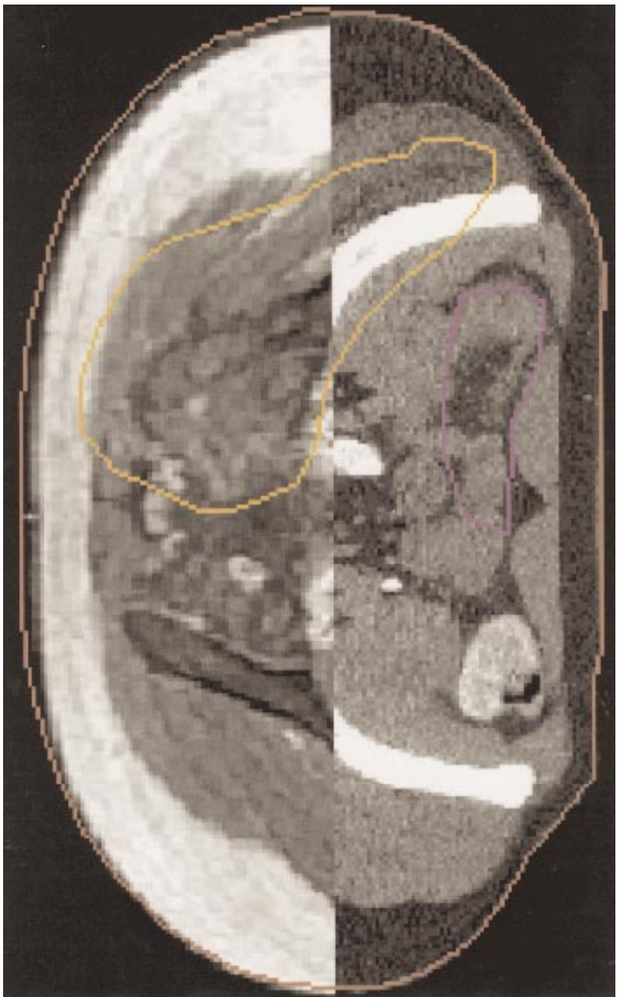


Figure 5.10 CT/MR image fusion used for treatment planning. The tumor and dose-limiting normal tissues are contoured on both CT and MR image sets and the composite contour is used for treatment planning.

dimension have been associated with an increased risk of recurrence in the postoperative setting.[7] CTV for tumors <10 cm in diameter should encompass the tumor with a longitudinal margin of at least 5 cm. For tumors >10 cm the CTV should include the tumor plus at least 7–10 cm longitudinal margin. Mediolateral margins for lesions in extremities can be extended to 2–3 cm where bone, interosseous membrane and facial planes define the boundary of an uninvolved compartment. Every attempt should be made to avoid circumferential radiation of an extremity to avoid development of edema due to complete obliteration of lymphatic egress. The minimum strip of soft tissue which should be spared is 2–3 cm; however, the more soft tissue which is spared from the target volume, the better the potential functional outcome.

Preoperative Dose

If concurrent chemotherapy is not to be used, 50 Gy given in 1.8–2.0 Gy fractions, and this has been shown to be adequate. This is followed by resection 2–3 weeks later. In the setting of concurrent neoadjuvant chemotherapy 2.5–3.5 Gy fractions can be used to total doses of 28–35 Gy followed by resection 10–14 days later.

Postoperative Target Volume

In the postoperative setting the GTV consists of the tumor bed, the surgical field and any potential spaces which require drainage or which contain postoperative fluid collections (i.e. seroma or hematoma). The surgical incision and all drain sites are included in this volume, which is considerably larger than the GTV in the preoperative setting. For tumors that are 10 cm or less an additional longitudinal margin of at least 5 cm is recommended. This volume constitutes the postoperative CTV. For tumors >10 cm the CTV should include the GTV plus an additional 7–10 cm longitudinal margin. Bone, interosseous membrane and intact fascia restrict the mediolateral extension of sarcoma such that mediolateral margins need not be greater than 3 cm. The surgical incision and all drain sites should be treated, and bolus should be used if necessary to eliminate skin-sparing at these sites due to nontangential exposure. Circumferential radiation of an extremity should be avoided if at all possible. Preferably one-third of the width of a limb should be spared, but whenever possible not less than 2–3 cm, in order to prevent severe extremity lymphedema.

Postoperative Dose

In the postoperative setting of negative margins at total dose of 63 Gy is routinely used at the NCI. The initial CTV is treated to 45 Gy. Subsequently the CTV is decreased to 2 cm beyond the GTV, and this second CTV is used to deliver the final 18 Gy for a total dose of 63 Gy. Daily fraction sizes of 1.8–2.0 Gy are used. It is recommended by some authors to decrease the total dose by 10% if concurrent chemotherapy is given. This has never been the policy at the NCI. If margins are microscopically positive the total dose should be increased to 66–70 Gy utilizing a CTV which is limited to the region of margin positivity plus 2 cm. For patients with gross tumor which is to be treated curatively with radiation alone, the total dose should be 72–76 Gy. In this setting a "shrinking-field" technique should be

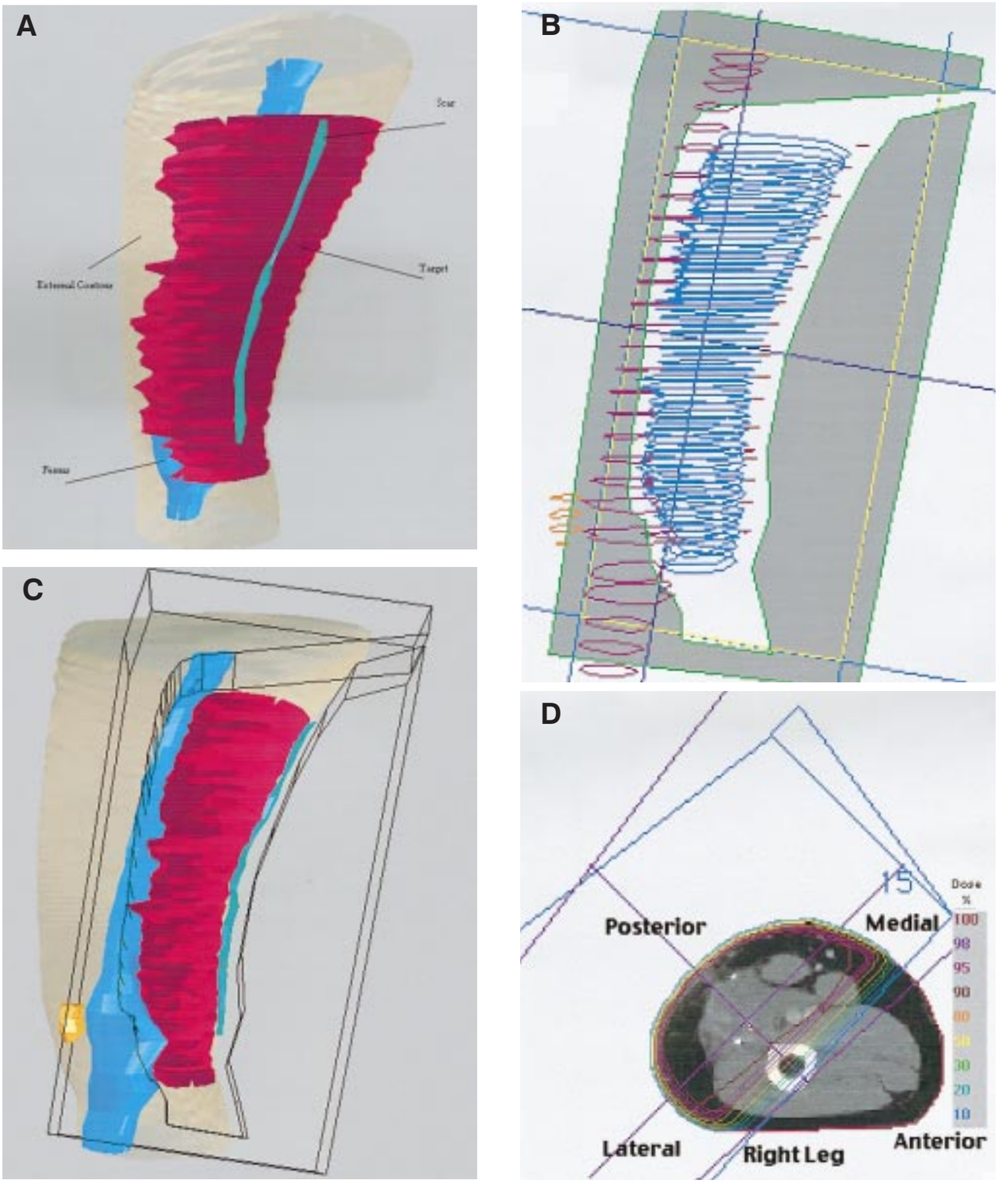


Figure 5.11 Three-dimensional treatment planning for a thigh sarcoma. In (**A**) a three-dimensional posterior/oblique projection displays the clinical target volume, the incision scar, the femur, and the external contour of the thigh. (**B**) and (**C**) show a beam's eye view of the target volume and computer-generated shaped blocks. Wire diagrams of the CT/MR contours (the block is shaded gray) are shown in (**B**) and three-dimensional surface contours are shown in (**C**). A cross-section showing the dose distribution through the tumor at the isocenter is shown in (**D**).

used. This consists of multiple consecutively smaller CTVs culminating in a volume which encompasses gross tumor with 1.0 cm margin.

Hands and Feet

Treatment of hands and feet requires special consideration if a good functional outcome is to result.

Hand

Sarcomas arising on the hand and wrist should be treated with the hand outstretched and flattened on a board; one is shown in Figure 5.12. An immobilization cast should be fabricated to ensure precise daily repositioning of the treated limb. Because tumors arising in the hand tend to be relatively small when diagnosed, and due to the limited volume of the hand, the normal margin guidelines for truncal and extremity sites do not necessarily apply. For resected lesions on the hand the CTV should include the surgical tumor bed, which should be demarcated by clips placed at the time of surgery plus 2 cm medially and laterally, and 4–6 cm longitudinally. The incision and any drain sites should be treated with bolus if necessary, to ensure that they receive full dose per fraction. Care must be taken to avoid treatment of the nailbeds and distal interphalangeal joints if possible. Sparing as much of the palmar aponeurosis as possible will help prevent the development of a flexion contracture. Circumferential treatment of the hand and fingers should be avoided, to prevent edema and contracture. If one limb of the arterial arcade of the hand can be spared, this may help reduce late soft-tissue and muscle atrophy. Arteriograms of the hand and wrist in the immobilized treatment position may be helpful in this regard. Treatment beams are usually parallel opposed in the dorsal/plantar direction. An example of the treatment technique used for a hand is shown in Figure 5.13.

Feet

The steeply sloping and irregular contours of the foot, and its relatively small size, pose a unique challenge with respect to achievement of a homogeneous dose distribution. Custom immobilization devices, complex compensators and sophisticated treatment planning should be routinely employed. Immersion of the foot in a waterbath is a technique which has been employed to achieve a homogeneous electron equilibrium within the target volume in the foot, which may vary considerably in tissue thickness. Lesions on the proximal portion of the foot are treated with beams which enter and exit over the lateral and medial surfaces. Lesions on the more distal aspect of the foot are treated with beams entering and exiting over the dorsal/ventral surfaces. Careful attention is paid to avoidance of treating the entire width of the plantar aponeurosis, otherwise a resulting flexion contracture could lead to a useless, painful, clubbed foot and ultimately a palliative amputation. Whenever possible the Achilles tendon, the heel, the sole, the toes and the nailbeds should be spared as long as treatment of the tumor or its bed will not be compromised. Electron beams can be useful in boosting scars, and in preventing full-thickness radiation if this is not desired. Bolus should be used over scars to ensure full dose unless high-energy electrons or tangential beams eliminate skin-sparing.

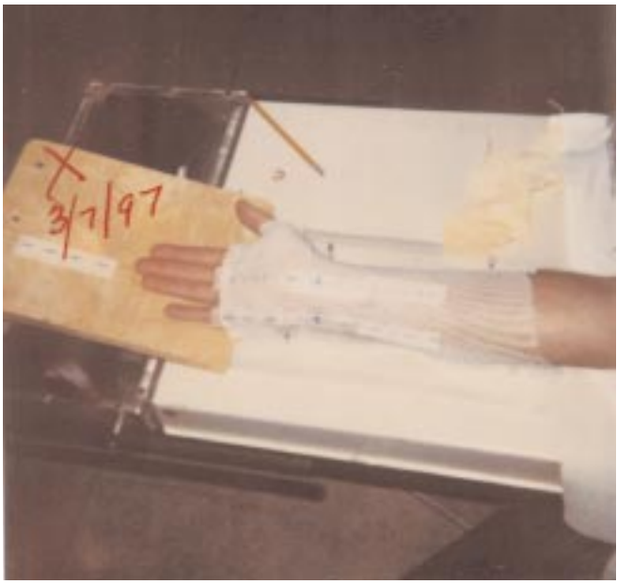
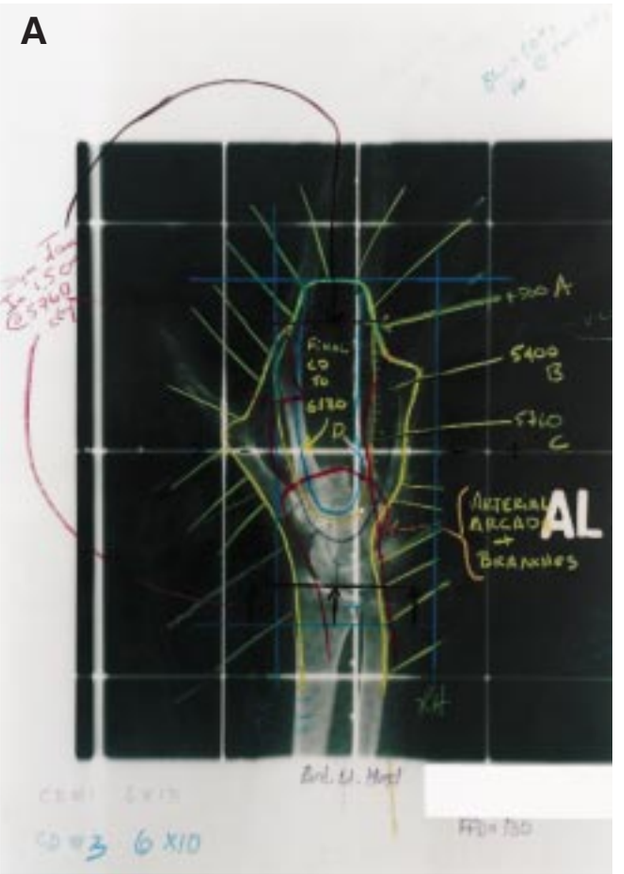
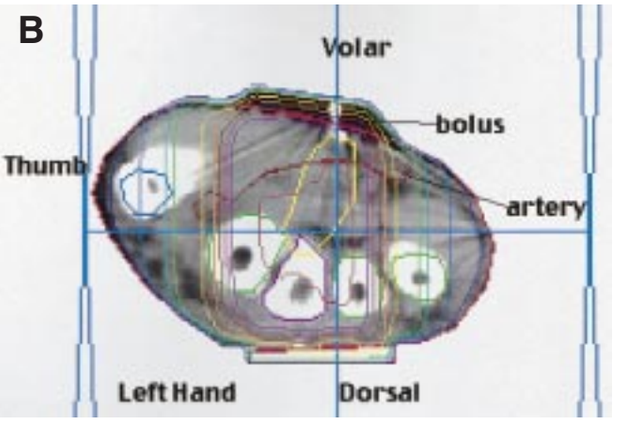
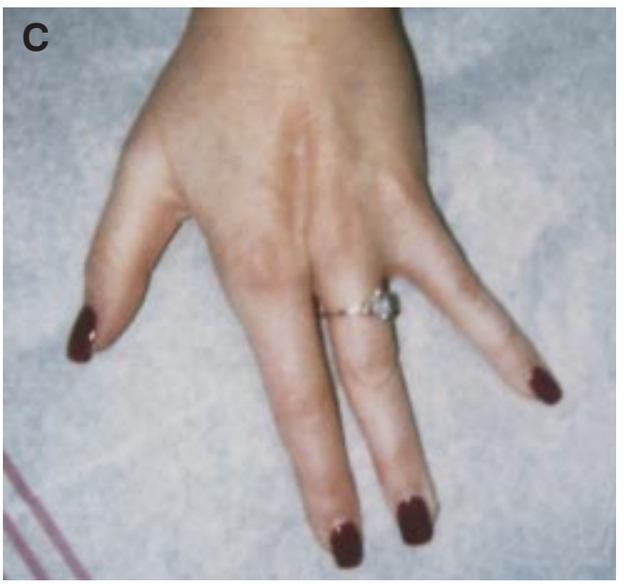


Figure 5.12 An immobilization device used for treatment of a hand sarcoma. The hand is in an outstretched and flat position to allow treatment with opposed anterior and posterior beams.







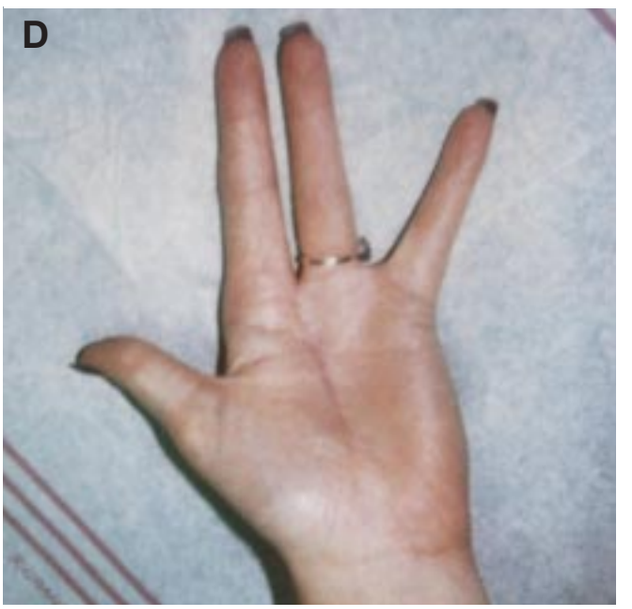


Figure 5.13 Treatment technique used to treat a synovial sarcoma of the hand following resection of the third finger and its metacarpal bone. An anterior simulation film is shown in (**A**). Note the mapping of the arterial supply of the hand shown in red, and the use of successive 'cone down' or so-called 'shrinking field' technique. One arterial limb feeding the arterial arcade is spared from the target volume completely. The initial target volume (**A**) received 4500 cGy; the first 'cone down' received 5400 cGy; the second cone down received 5760 cGy; and the final clone down volume (**D**), which corresponds to the tumor bed, received a total of 6120 cGy. A cross-sectional view of the dose distribution is shown in (**B**); note the bolus which eliminates skin-sparing over the scar. Bolus is also useful to ensure full dose to the tumor bed which may lie close to the skin surface in a relatively thin structure such as a hand. An excellent cosmetic and functional result is seen in (**C**) and (**D**) approximately 4 years following treatment. The patient is able to type 50 words per minute.

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