Radiotherapy and Oncology 75 (2005) 48–53
www.elsevier.com/locate/radonline

Phase III randomised trial

Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma

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Abstract

***Background and Purpose*: This study compared late radiation morbidity in patients with extremity soft tissue sarcoma randomized to treatment by pre- (50 Gy) or postoperative (66 Gy) radiotherapy in combination with surgery. The morbidities evaluated included fibrosis, joint stiffness and edema at 2 years following treatment. The impact of morbidity on patient function as measured by the Musculoskeletal Tumor Rating Scale (MSTS) and the Toronto Extremity Salvage Score (TESS) was also evaluated.**

***Patients and methods*: 129 patients were evaluated. Toxicity rates were compared by treatment arm using the Fisher's exact test. Function scores by toxicity were analyzed using the Wilcoxon rank sum test. Multivariate logistic regression was used to evaluate the joint effect of treatment arm, field size, and dose on subcutaneous tissue fibrosis, joint stiffness and edema.**

***Results*: 27 of 56 patients (48.2%) in the postoperative arm compared to 23 of 73 (31.5%) in the preoperative arm had grade 2 or greater fibrosis ($P=0.07$). Although not statistically significant, edema was more frequent in the postoperative arm, 13 of 56 (23.2%) versus 11 of 73 (15.1%) in the preoperative arm, as was joint stiffness, 13 of 56 (23.2%) versus 13 of 73 (17.8%). Patients with significant fibrosis, joint stiffness or edema had significantly lower function scores on both measures (all *P*-values <0.01). Field size was predictive of greater rates of fibrosis ($P=0.002$) and joint stiffness ($P=0.006$) and marginally predictive of edema ($P=0.06$).**

***Conclusions*: Patients treated with postoperative radiotherapy tended to have greater fibrosis. Fibrosis, joint stiffness and edema adversely affect patient function.**

Keywords: Radiotherapy; Toxicity; Randomized trial; Extremity soft tissue sarcoma

Patients with extremity soft tissue sarcoma are commonly treated with limb preservation surgery in combination with adjuvant radiotherapy [13,14,16,19,22,23,26,32,33]. While adjuvant radiotherapy may be given with external beam or brachytherapy, external beam techniques continue to be used at most centers in Europe and North America [13–15,21,26,32]. These modalities achieve optimum local tumor control; however, physical disability and reduced quality of life may result from treatment morbidity [7,15]. In patients with extremity soft tissue sarcoma, these morbidities may include major wound complications [3,4,15,18,20] and late radiation effects such as subcutaneous tissue fibrosis, edema, joint stiffness, and bone changes including osteoradionecrosis and fracture [2,5,15,17,21,25].

There is limited documentation of the effects of late radiation morbidity on extremity function in soft tissue sarcoma patients in the literature. Three retrospective studies evaluated function in relation to radiation dose and morbidity but these studies included patients treated as early as 1975 in one study and 1983 in the remaining studies [14,21,25]. With the advent of computerized tomography

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radiotherapy planning in the 1980s and new methods of treatment delivery, it is difficult to evaluate the results of these published studies based on more current treatment methods. As a secondary objective of the SR.2 trial, the current study evaluated the impact of two different regimes of external beam radiotherapy in the development of clinically significant radiation morbidity, specifically subcutaneous fibrosis, joint stiffness and edema, as reported at 2 years following treatment. We hypothesized that patients treated with postoperative radiotherapy would have greater radiation morbidity and that patients with greater morbidity would have poorer function.

Patients and methods

Patients recruited to the SR.2 study formed the sample for this study, and the methodological details of this multicentered, randomized trial are described in detail by O'Sullivan et al. [15]. In brief, SR.2 was a trial in which patients greater than 16 years of age with curable extremity soft tissue sarcoma were randomized to receive preoperative external beam radiotherapy (pre-op) followed by limb preservation surgery or surgery followed by postoperative radiotherapy (post-op). The primary outcome was the incidence of major wound complications according to predefined criteria that included return to the operating room or continued deep packing at 4 months post-surgery. Ethical approval was received by the Human Subject Review Committee at each participating institution.

A total of 190 patients (94 on pre-op arm and 96 on post-op arm) were randomized to the SR.2 study. Among them, 181 (92 on pre-op arm and 89 on post-op arm) received either pre- or postoperative Phase I external beam radiotherapy in accordance with the SR.2 protocol. Because of the variation in the scheduling of clinical visits, the patients were considered as having 2-year follow-up in this paper if they had a clinical follow-up visit between 21 and 27 months from the end of the Phase I radiation treatment. The toxicity and function data assessed at these visits were included in this analysis. If a patient had more than one visit during this 6-month interval, only the data on the earliest visit were included. One hundred and sixty patients were still under follow-up (respectively, 83 on pre-op arm and 77 on post-op arm) at 21 months after the completion of radiation treatment and 152 (79 on pre-op arm and 73 on post-op arm) at 27 months. Based on the definition above, 59 patients (19 on pre-op arm and 33 on post-op arm) were excluded from this analysis because they died prior to the 2-year follow-up visit, were lost to follow-up due to illness from treatment, progressive disease or for some other unknown reason. These exclusions included 31 patients still under follow-up at 21 months (10 on preoperative radiotherapy and 21 on postoperative radiotherapy) who had missing toxicity data for reasons identified above. Table 1 provides the details of the 73 patients randomized to preoperative radiotherapy and 56 patients randomized to postoperative radiotherapy who are included in this study. There were more males and younger patients treated by preoperative radiotherapy and more patients on the preoperative arm had large tumor size (>10 cm). No difference between the two treatment arms was, however, statistically significant. As the tumor pathology was not re-reviewed, the tumor typing reflects the original classification system used [15].

Surgery and radiotherapy were separated by 3–6 weeks in both arms of the trial. An initial volume 5 cm proximal and distal to the tissues at risk (Phase I) received 50 Gy in 2 Gy fractions followed by a volume reduction to 2 cm surrounding the target (Phase II) as required by the protocol. Phase II (16–20 Gy) was required for all postoperative cases, but in the preoperative cases only if pathologic assessment showed tumor at the inked resection margin of the surgical specimen. When indicated in the preoperative arm, Phase II was not administered until after the wound was healed. A longitudinal strip of skin and subcutaneous tissue of an extremity was spared for at least 50% of the course unless it involved a reduction of the radiotherapy margin around the target area to less than 2 cm at any point that was not confined by an intact fascial boundary. Planning, dosimetry, and dose prescription followed International Commission on Radiation Units (ICRU) guidelines [11] and all fractions and fields were treated daily. Radiotherapy treatment plans were simulated and limb immobilization and computerized tomography planning was encouraged. Plan documentation included three cross-sectional isodose distributions depicting the dose at the center and the proximal and distal limits of the high dose volume. Center quality assurance review of the Phase I radiotherapy plan was required within 3 days of commencement of radiotherapy. The intent of surgical resection was complete tumor removal with a margin of normal tissue surrounding the tumor while preserving as much functional tissue as possible.

Late subcutaneous fibrosis and joint stiffness arising directly from the radiation treatment were assessed using the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) late toxicity scoring criteria [5]. Edema was measured according to the criteria of Stern [24]. The scoring criteria are presented in Tables 2a and 2b. A priori, it was determined that toxicity ratings of grade 2 or greater were clinically significant.

Patient function and physical disability and general health status were evaluated using the Musculoskeletal Tumor Society Rating Scale (MSTS) [10] and The Toronto Extremity Salvage Score (TESS) [6,9]. The Musculoskeletal Tumor Society Rating Scale is a clinician-rated measure of impairment [8,29,30]; that is, mainly reflecting problems at the organ level. It includes pain, range of motion, strength, joint stability, joint deformity, overall acceptance of the surgery, and a global rating of function. The Toronto Extremity Salvage Score is a patient-completed measure of physical disability [8,29,30]; that is, reflecting patient's ratings of the difficulty experienced in activities of daily living, including self-care, mobility and role functions. The Musculoskeletal Tumor Society Rating Scale ranges from 0 to 35 and the Toronto Extremity Salvage Score ranges from 0 to 100. For both measures, higher scores reflect better function.

Table 1
Patient and tumor characteristics of 129 patients evaluable for late radiation morbidity

Characteristic	Categorization	Pre-op, *n* (%)[a]	Post-op, *n* (%)	*P*-value
Gender	Female	33 (45)	29 (52)	0.48
	Male	40 (55)	27 (48)	
Age (yrs) at allocation	<50	26 (36)	26 (46)	0.36
	≥ 50-<70	29 (40)	21 (38)	
	≥ 70	18 (24)	9 (16)	
Stratification tumor size (cm)	≤ 10	48 (66)	43 (77)	0.24
	>10	25 (34)	13 (33)	
Lesion presentation	Primary	64 (88)	50 (89)	1.00
	Recurrent	9 (12)	6 (11)	
Compartment status (intra vs. extra)	Intra-compartmental	22 (30)	14 (25)	0.52
	Extra by tumor growth	10 (14)	5 (9)	
	Extra by iatrogenic spread	5 (7)	2 (4)	
	Extra de novo	36 (49)	35 (63)	
Tumor Grade	Low	15 (21)	13 (23)	0.83
	Intermediate/high	58 (79)	43 (82)	
Histologic subtype	MFH	21 (29)	14 (25)	0.78
	Liposarcoma	22 (30)	14 (25)	
	Leiomyosarcoma	6 (8)	6 (11)	
	Other histology	24 (33)	22 (39)	
Anatomic site (extremity)	Proximal upper	10 (14)	6 (11)	0.97
	Distal upper and elbow	7 (10)	6 (11)	
	Proximal lower and knee	37 (51)	30 (54)	
	Distal lower	19 (26)	14 (25)	
Tumor depth	Superficial and deep to fascia	16 (22)	14 (25)	0.27
	Deep to fascia	45 (62)	27 (48)	
	Superficial to fascia	12 (16)	15 (27)	
Final resection margins (after protocol surgery)	Missing	1 (1)	0 (0)	0.88
	Negative gross and micro	63 (86)	50 (89)	
	Negative on gross exam, positive on micro exam	9 (13)	6 (11)	
Total evaluable		73 (100)	56 (100)	

Pre-op, preoperative radiotherapy; Post-op, postoperative radiotherapy; MFH, malignant fibrous histiocytoma; exam, examination; micro, microscopic; *n*, number of cases. *P*-values were calculated by Fisher's exact test.
[a] Due to rounding total percentages do not always equal 100.

Statistical analysis

All patients were analyzed in their assigned groups based on the intention to treat principle. The proportion of patients experiencing grade 2 or greater subcutaneous fibrosis, joint stiffness and edema was compared by treatment arm using the Fisher's exact test. Function as measured by the Musculoskeletal Tumor Society Rating Scale [10] and The Toronto Extremity Salvage Score [6,9] was compared by grade of radiation toxicity using the Wilcoxon rank sum test [31] as the data were not normally distributed. Factors thought to be associated with radiation toxicity, such as fibrosis, joint and edema dichotomized at grade 2, were evaluated using a multivariate logistic regression model. Specifically, we included simultaneously in the regression models radiation field size (width$\times$length) in cm^2 and the maximum target absorbed dose ($D_{T,max}$) defined as the 2 cm^2 area that received the highest dose on any of the three cross-sectional isodose distributions [11].

Table 2a
EORTC/RTOG Late Radiation Toxicity Criteria [5]

Tissue	Grade 0	Grade 1	Grade 2	Grade 3
Subcutaneous fibrosis	None	Slight fibrosis; subcutaneous fat loss	Moderate fibrosis; slight field contracture	Severe fibrosis; field contracture $>10\%$
Joint	None	Mild stiffness; slight range of motion loss	Moderate stiffness, pain, range of motion loss	Severe stiffness, pain, range of motion loss

Table 2b
Stern's Rating Scale for Edema [24]

Score	Rating
0	None
1	Mild (but definite swelling)
2	Moderate
3	Severe (considerable swelling)
4	Very severe (skin shiny and tight ± skin cracking)

P-values of 0.05, based on two-sided testing, were considered to be statistically significant with no adjustment for multiple comparisons.

Results

As shown in Table 3, a greater proportion of patients treated with postoperative radiotherapy had grade 2 or greater subcutaneous fibrosis (48.2 versus 31.5%, $P=0.07$ and 95% confidence interval (CI) for the difference in the proportions −0.0002 to 0.3; joint stiffness (23.2 versus 17.8%, $P=0.51$, 95% CI 0.09–0.19); and edema (23.2 versus 15.1%, $P=0.26$, 95% CI 0.05–0.22), although the proportionate difference was not statistically significant for either joint stiffness or edema and only trended towards significance for fibrosis. There was no statistically significant difference in patient function by treatment arm as measured by the TESS or MSTS in the current study (pre-op mean 85.1 versus post-op mean 81.3; $P=0.17$ and pre-op mean 29.9 versus post-op mean 28.0; $P=0.08$, respectively). Patients who had grade 2 or greater fibrosis, joint stiffness and edema reported significantly greater physical disability as measured by the Toronto Extremity Salvage Score (fibrosis 77.1 versus 87.0, $P=0.001$; joint stiffness 69.4 versus 86.4, $P=0.001$; edema 71.9 versus 85.0, $P=0.01$ and significantly greater impairment as measured by Musculoskeletal Tumor Society Rating Scale (fibrosis 27.7 versus 30.5, $P=0.002$; joint stiffness 24.2 versus 30.8, $P=0.001$; edema 21.9 versus 30.4, $P<0.001$). These results are detailed in Table 4.

In logistic regression, only field size ($P=0.002$) was a risk factor for subcutaneous fibrosis; $D_{T,max}$ ($P=0.23$) and pre- versus postoperative radiotherapy were not significant ($P=0.58$). Similarly, joint stiffness was predicted only by field size ($P=0.006$) and there was a trend toward field size predicting edema ($P=0.06$). In the model for each outcome, treatment arm was confounded by field size and $D_{T,max}$ dose; that is, field sizes were larger when treated by postoperative radiotherapy and the irradiation dose was higher with postoperative radiotherapy.

Table 3
Late radiation toxicity by treatment arm

		Preoperative radiotherapy, $n=73$ (%)	Postoperative radiotherapy, $n=56$ (%)
Subcutaneous fibrosis	<2	50 (68.5)[a]	29 (51.8)
	>2	23 (31.5)	27 (48.2)
Joint	<2	60 (82.2)	43 (76.8)
	>2	13 (17.8)	13 (23.2)
Edema	<2	62 (84.9)	43 (76.8)
	>2	11 (15.1)	13 (23.2)

[a] $P=0.07$ calculated by Fisher's exact test.

Discussion

This study of patients randomized to pre- or postoperative radiotherapy suggests that patients treated with postoperative radiotherapy by contemporary standards of care during the accrual period proportionately have more late radiation toxicity, specifically subcutaneous fibrosis, joint stiffness and extremity edema than the preoperative radiotherapy group. However, the proportion in the postoperative group was not significantly different from those treated with preoperative radiotherapy due to low power. Toxicity was a secondary endpoint of the SR.2 trial and, with the current sample sizes, the power to detect the observed differences respectively would be 40% for fibrosis, 12% for joint stiffness and 22% for extremity edema. Radiation morbidity adversely affects patient function as measured by the Musculoskeletal Tumor Society Rating Scale [10] and the Toronto Extremity Salvage Score [7,9].

For this study, radiation morbidity is defined at a single point in time, 2 years following treatment. Although the 90-day rule has been described as the period after which late radiation toxicity is considered to have occurred [27], fibrosis has been shown to develop over a 2-year period with uncertain progression after this time [3]. We, therefore, chose 2-year follow-up for this analysis. This decision resulted in different numbers of patients in the treatment arms than for the primary outcome, wound complications [13], and for reporting of functional outcomes [12] for a variety of reasons including death, loss to follow-up, inability to complete the TESS or MSTS or missing toxicity data. If patients failed to return to follow-up because of severe toxicity (informative missing) the results may be biased; however, the effect would be to underestimate the severity in the postoperative radiotherapy arm and, hence, enlarge the difference between the two treatment groups. There was no significant difference in patient function by treatment arm as previously reported (12).

The proportion of patients with clinically significant (i.e. grade 2 or greater) subcutaneous fibrosis, joint stiffness and edema is similar to the rates reported in soft tissue sarcoma by others. Stinson et al. [25] reported that 57% of cases ($n=145$) had tissue induration, 20% had joint contracture and 19% had 2+ or greater edema. The doses and fractionation schedule were slightly different than the current study; however, the total dose and $D_{T,max}$ for all the cases in both studies were minimally different. These authors [25] also found that inclusion of more than 50% of the joint in the radiation field was related to joint contracture and radiation doses of greater than 63 Gy at 1.8 Gy per fraction with tumors in the lower extremity were associated with moderate to severe edema. Fibrosis was associated with field length and lower extremity tumors. Robinson et al. [21] reported on 54 lower extremity soft tissue sarcoma patients treated with surgery and/or radiotherapy (13 cases of whom were

Table 4
Function by grade of radiation morbidity and treatment arm

		Musculoskeletal Tumor Society Rating Scale			Toronto Extremity Salvage Score		
		n	mean (sd)	*P*[a]	*n*	mean (sd)	*P*
Subcutaneous fibrosis	<2	61	30.5 (7.7)	0.002	54	87.0 (18.2)	0.001
	>2	47	27.7 (7.5)		45	77.1 (19.4)	
Joint stiffness	<2	85	30.8 (7.1)	0.001	76	86.4 (17.0)	0.001
	>2	23	24.2 (7.9)		23	69.4 (21.0)	
Edema	<2	87	30.4 (7.2)	<0.001	80	85.0 (18.3)	0.01
	>2	21	21.9 (8.6)		19	71.9 (20.3)	
Treatment arm	Pre-op	60	29.9 (7.8)	0.08	64	85.1 (19.3)	0.17
	Post-op	63	28.0 (8.6)		66	81.3 (17.2)	

[a] *P*-values were calculated by Wilcoxon rank sum test.

determined to have received high-dose radiotherapy defined as those treated with unconventional hypo- or hyperfractionated regimes or very high doses) and found that 16 (30%) had lymphedema, 39 (72%) had some restriction of movement in evaluated joints and 12 (22%) had severe restriction of movement. Radiotherapy doses above 60 Gy were associated with fibrosis and worse function [21]. Zagars et al. [34], who retrospectively reviewed patients with sarcoma from multiple anatomical sites, reported significant late radiotherapy-related complications in 33 patients, 11 treated with preoperative radiotherapy and 22 treated with postoperative radiotherapy (though the actual sample size of the original 517 available for evaluation of late toxicity and the time at which toxicity was reported were not stated). The preoperative radiotherapy dose was 50 Gy and the postoperative dose ranged from 60 to 70 Gy. The complications reported included soft tissue necrosis, bone fracture, osteonecrosis, brain necrosis, edema and fibrosis. Only the sequencing of treatment was significant in predicting late complications. Finally, while it is difficult to interpret the intra-operative radiotherapy plus external beam radiotherapy approach compared to external beam radiotherapy alone, results from van Kampen and colleagues [28] also found similar rates of treatment morbidity. Despite the differences in these studies, it seems clear that increasing field size, whether represented by field width multiplied by field length or by field length alone, is associated with increased subcutaneous tissue fibrosis.

In the current study, patients with fibrosis, joint stiffness, and edema greater than grade 2 had consistently and statistically significant lower functional scores. These findings are in keeping with Stinson et al. [25] who reported that high radiation dose was correlated with pain, decreased strength and decreased range of motion, three of the seven evaluated features of the Musculoskeletal Tumor Society Rating Scale [10]. Robinson et al. [21] found range of motion and muscle strength to be negatively influenced by fibrosis and edema. 'Function assessment' (items such as mobility, self-care, activities of daily living, vocation and leisure that were more similar to the Toronto Extremity Salvage Score [6,9]) was negatively impacted by radiation dose. Karasek et al. [14], reporting on 41 extremity and trunk soft tissue sarcoma patients, found that the volume of tissue irradiated to greater than 55 Gy was associated with poorer function (where the measure developed by the authors included: mobility, pain, edema, strength, gait, upper extremity function, fibrosis and skin changes, with aggregate scores collapsed to four categories ranging from poor to excellent).

The current study suggests that due to the differences in field size, patients treated with preoperative radiotherapy doses may have less late radiation toxicity as measured by subcutaneous fibrosis, edema, and joint stiffness than patients treated by the higher dose and volume postoperative radiotherapy techniques. These risks must be balanced against the risk of wound complications and their impact on function in patients treated with preoperative radiotherapy.

Jung et al. [12] suggest that there might be a life-long risk of developing late complications. These ongoing late complications may result from processes as yet undefined that may trigger subclinical residual injury that manifests as a clinically significant late effect. Andreassen et al. [1] have suggested that models based on multiple genetic markers may predict normal tissue responses to radiotherapy. Only ongoing follow-up of patients treated with radiotherapy will facilitate understanding of this phenomenon. Furthermore, as radiotherapy delivery methods continue to develop and improve it will be important to evaluate their effect on toxicity.

Acknowledgements

This study was funded by the National Cancer Institute of Canada—Clinical Trials Group, Queen's University, Kingston, Ont., Canada. Dr Davis is supported by a Health Career Award from the Canadian Institutes of Health Research.

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Received 4 April 2004; received in revised form 13 December 2004; accepted 22 December 2004; available online 14 March 2005

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