Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial

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Summary

Background External-beam radiotherapy (delivered either preoperatively or postoperatively) is frequently used in local management of sarcomas in the soft tissue of limbs, but the two approaches differ substantially in their potential toxic effects. We aimed to determine whether the timing of external-beam radiotherapy affected the number of wound healing complications in soft-tissue sarcoma in the limbs of adults.

Methods After stratification by tumour size (≤10 cm or >10 cm), we randomly allocated 94 patients to preoperative radiotherapy (50 Gy in 25 fractions) and 96 to postoperative radiotherapy (66 Gy in 33 fractions). The primary endpoint was rate of wound complications within 120 days of surgery. Analyses were per protocol for primary outcomes and by intention to treat for secondary outcomes.

Findings Median follow-up was 3·3 years (range 0·27–5·6). Four patients, all in the preoperative group, did not undergo protocol surgery and were not evaluable for the primary outcome. Of those patients who were eligible and evaluable, wound complications were recorded in 31 (35%) of 88 in the preoperative group and 16 (17%) of 94 in the postoperative group (difference 18% [95% CI 5–30], p=0·01). Tumour size and anatomical site were also significant risk factors in multivariate analysis. Overall survival was slightly better in patients who had preoperative radiotherapy than in those who had postoperative treatment (p=0·0481).

Interpretation Because preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy, the choice of regimen for patients with soft-tissue sarcoma should take into account the timing of surgery and radiotherapy, and the size and anatomical site of the tumour.

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Introduction

Local management of adult soft-tissue sarcoma generally requires surgery combined with radiotherapy. The usual radiation protocols are preoperative or postoperative external-beam treatment, or brachytherapy.[1–5] The aim of every strategy is to have maximum control of local tumours while preserving function. For external-beam treatment, however, preoperative radiotherapy requires smaller field sizes[6] and lower doses.[7,8] Lower doses are usually preferred because higher doses result in worse functional outcome.[9] Features such as tumour size and grade and depth of origin are associated with worse prognosis,[10] and preoperative radiotherapy is more likely to be chosen in such lesions than postoperative radiotherapy.[2]

Despite potential advantages of preoperative radiotherapy, the higher rates of wound complication cause concern.[11–15] However, high rates of surgical complications have also been reported without radiation, especially in complicated resections.[16] Therefore, use of preoperative radiation for more advanced lesions could contribute to the reported increase in wound complication rates in patients with soft-tissue sarcoma.

We did a multicentre randomised controlled trial to determine whether scheduling of external beam radiotherapy (preoperative *vs* postoperative) affected the rate of wound complications.

Methods

Patients

The trial opened to accrual in October, 1994, and closed in December, 1997, after 190 patients had been randomised. We closed the trial before completion of planned accrual (266 cases) because a planned, preliminary analysis by a data-monitoring committee determined that the primary outcome showed a significant difference. Randomisation was by computer-generated block design issued through a telephone call by which the participating centre confirmed the patient's eligibility. The people who did the randomisation were not involved in treatment of patients or analysis of the data.

Patients were eligible if they had soft-tissue sarcoma originating in a limb (defined as extending from the medial border of the scapula to the fingers or from the iliac crest to the toes) without metastasis. An approved local reference pathologist verified the diagnosis before randomisation, and lesions were graded in a subsequent central pathology review. We determined the need for combined surgery and radiotherapy and for additional eligibility and exclusion criteria before randomisation (panel). The research ethics committees at all participating centres approved the study, and all patients gave written informed consent before enrolment.

Endpoints

The primary endpoint was presence or absence of a major wound complication—defined as a secondary operation under general or regional anaesthesia for wound repair (debridement, operative drainage, and secondary wound closure including rotationplasty, free flaps, or skin grafts),

or wound management without secondary operation. Wound management included an invasive procedure without general or regional anaesthesia (mainly aspiration of seroma), readmission for wound care such as intravenous antibiotics, or persistent deep packing for 120 days or longer. On the basis of these predefined criteria, we prospectively assessed all patients for the cumulative frequency of wound complications that had developed up to 4 months after surgery. To assess the primary endpoint, patients were followed up weekly for the first month, every second week for the second month, and monthly thereafter for 3 months. We could not assess patients for the primary endpoint if no surgery had been undertaken or if an amputation had been done.

Secondary endpoints were assessed in all eligible patients, and included local control, metastatic failure, progression-free survival, and overall survival. Acute toxic effects arising on the skin as a direct result of radiation treatment were assessed with the acute scoring criteria of the European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group .[17]

We assessed patients' function and general health with the Musculoskeletal Tumor Society rating scale,[18] the Toronto extremity salvage score,[19,20] and the short form-36.[21]

Procedures

Surgery and radiotherapy were done 3–6 weeks apart in both groups. We initally radiated a volume of 5 cm proximal and distal to the tissues at risk (phase I) with 50 Gy given in 2 Gy fractions. We then reduced the volume to 2 cm around the target (phase II), as required by protocol. All patients in the postoperative group were to have phase II treatment (16–20 Gy); patients in the preoperative group had such treatment only if pathological assessment showed tumour cells at the resection margin. When indicated in the preoperative group, phase II was not given until after the wound had healed. We left a longitudinal strip of skin and subcutaneous tissue of a limb untreated for at least half of the course, unless it reduced the radiotherapy margin around the target region to less than 2 cm at any point that was not confined by an intact fascial boundary. Planning, dosimetry, and dose prescription were done in accordance with International Commission on Radiation Units guidelines,[22] and all fractions and fields were given daily. We simulated radiotherapy treatment plans and encouraged immobilisation of limbs and planning with CT. Quality assurance of the phase-I radiotherapy plan was required within 3 days of start of radiotherapy.

The surgical goal was to achieve resection margins without tumour present on gross or microscopic review, while preserving as much functional tissue as possible. In some patients, tissue transfer techniques were needed to close the wound. However, surgeons agreed to disregard the radiation protocol when planning resection and wound closure. Prophylactic antibiotics and suction drains were used in all patients.

Prerandomisation eligibility and exclusion criteria

Eligibility criteria
Need for combined radiotherapy and surgery*
Diagnosis of soft-tissue sarcoma by an approved reference pathologist
First or recurrent presentations
Age >15 years
Written informed consent
Chest CT
Local CT or MRI

Exclusion criteria
Previous chemotherapy
Previous radiotherapy to the local site
Chemotherapy needed for this soft-tissue sarcoma
Age <16 years
Presence of regional or distant metastasis,
Previous or concurrent malignant disease
Histologies generally treated with chemotherapy
  Embryonal and alveolar rhabdomyosarcoma
  Soft-tissue osteosarcoma and Ewings' sarcoma
  Primitive neuroectodermal tumour
Benign histologies
  Dermatofibrosarcoma protruberans
  Aggressive fibromatosis

*If tumour, or surgically contaminated tissues in patients with incomplete excision, could not be excised with a minimum of 2 cm of healthy tissue or an intact fascial plane.

Statistical analysis

Patients were stratified before randomisation by maximum tumour dimension (≤10 cm or >10 cm). We used Fisher's exact test to compare rates of wound complication and acute toxic effects between treatment groups, and logistic regression to compare postoperative with preoperative groups while controlling for differences in baseline covariates between groups that might affect wound healing. A stepwise procedure was used to determine variables that were significantly related to the outcome. When all covariates were included, only those with a p value of less than 0·05 remained in the final model. We also assessed potential treatment-by-covariate interactions in the final logistic model. We analysed time-to-event endpoints with Kaplan-Meier estimate,[23] and did comparisons with the log-rank test.

We used a second exploratory logistic-regression model to assess the potential association of various factors on wound complication. The model included additional clinically relevant covariates that were obtained after randomisation at the time of surgery. Such covariates included substitution of the three-dimensional estimate of the resection specimen in place of maximum tumour size and addition of two other variables—depth of tumour as superficial or deep to the compartmental fascia, and primary or non-primary wound closure.

Since the Musculoskeletal Tumor Society rating scale, Toronto extremity salvage score, and short form-36 sub-scale scores were not normally distributed, we used Wilcoxon's test[24] to compare measures between treatment groups at the time of randomisation, and at 6 weeks, 3 months, 6 months, and 12 months after surgery.

We assumed a rate of preoperative radiotherapy wound complications of about 30% on the basis of published work. We thus needed 133 eligible and evaluable patients in each group to have 80% power to detect a 15% decrease in wound complication rate in the preoperative group with a two-sided 5% level test. We did a planned interim analysis for when half the data for assessment of wound complications was available (ie, the first 133 patients). The data and safety monitoring committee of the National Cancer Institute of Canada Clinical Trials Group decided that recruitment should be stopped if a significance level of 0·0056 was obtained in the analysis of the primary outcome. Analysis was done per protocol for the primary outcome, and by intention to treat for other outcomes.

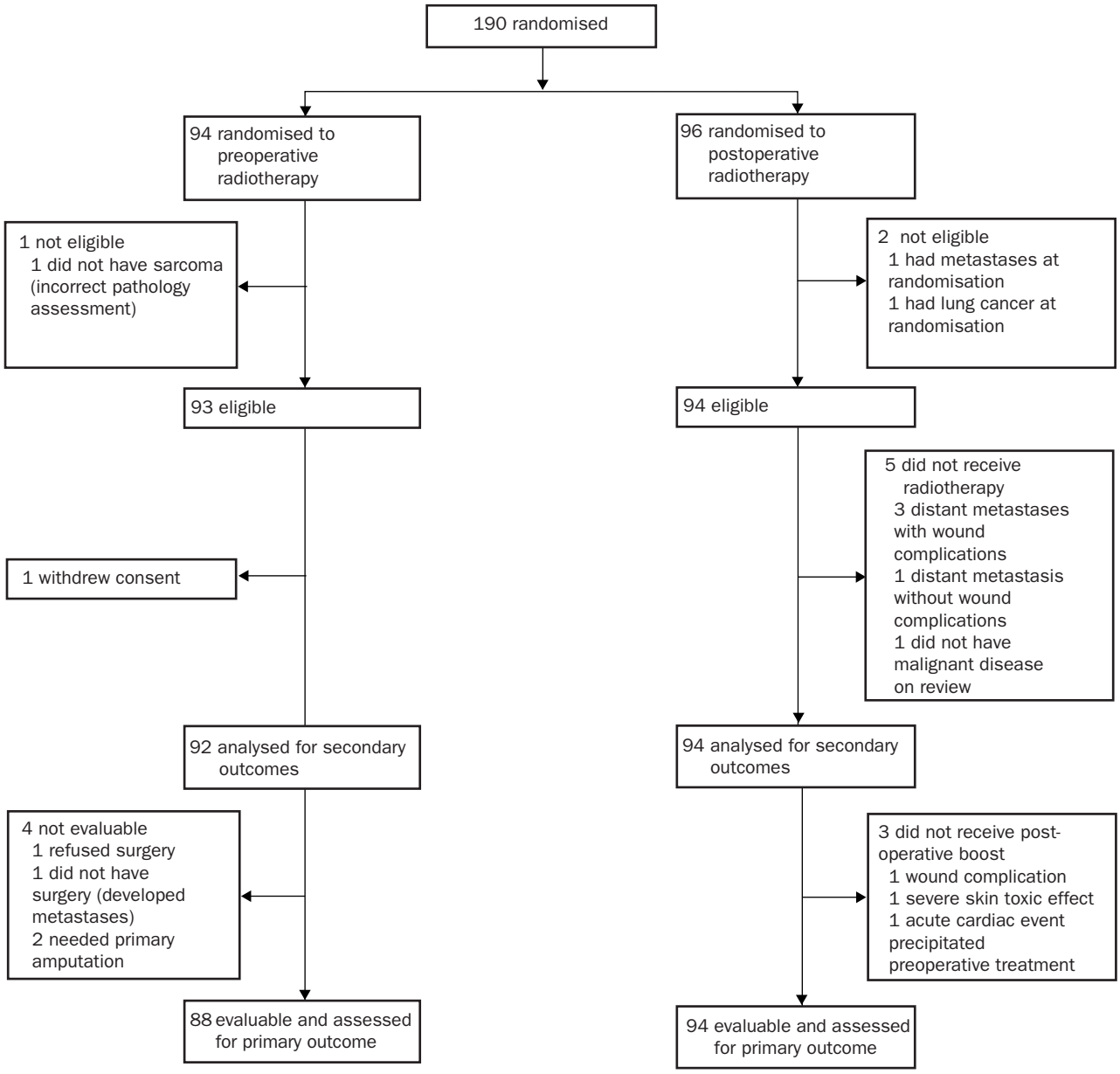

Figure 1: **Trial profile**

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We randomly assigned 94 patients to preoperative and 96 to postoperative radiotherapy (figure 1). Quality assurance was done in 161 (88%) of 184 patients planned for radiotherapy (two patients planned for radiotherapy did not receive it). Of these, 153 (95%) met phase I protocol requirements, including five who had their plans modified because of the quality assurance review. Four of 88 patients in the preoperative group had negative resection margins, but received a postoperative boost (phase II) and were protocol violations.

Table 1 shows the characteristics of patients and tumours. Potential healing detractors did not differ between groups, including history of tobacco use (preoperative 16 [18%], postoperative 15 [16%], corticosteroid use (none *vs* one [1%]), diabetes (eight [9%] *vs* 12 [13%]), being a vegetarian (one [1%] *vs* one [1%]), or history of peripheral vascular disease (two [2%] *vs* two [2%]). The wound status before randomisation also did not differ: the rate of tumour fungation or infection was five (6%) in the preoperative and eight (9%) in the postoperative group.

Median follow-up was 3·3 years (range 0·27–5·6), and all but five patients were followed up for the primary endpoint (figure 1). Three of 89 patients in the postoperative group who received radiotherapy did not receive the postoperative boost (phase II) because of a wound complication that manifested during radiotherapy (one patient), severe skin toxic effects in phase I (one), or an acute cardiac event that delayed sarcoma surgery and the patient received preoperative treatment (one). Positive resection margins were recorded in 14 of 88 evaluable preoperative patients, and ten of these received a

Characteristic	Preoperative (n=88)	Postoperative (n=94)
Sex		
Female	40 (45%)	43 (46%)
Male	48 (55%)	51 (54%)
Age at allocation (years)		
<50	30 (34%)	44 (47%)
⩾50 to <70	38 (43%)	33 (35%)
⩾70	20 (23%)	17 (18%)
Tumour size		
⩽10 cm	57 (65%)	63 (67%)
>10 cm	31 (35%)	31 (33%)
Lesion presentation		
First	79 (90%)	87 (93%)
Recurrent	9 (10%)	7 (7%)
Compartment status		
Intracompartmental	45 (51%)	48 (51%)
Extracompartmental by tumour growth	26 (30%)	26 (28%)
Extracompartmental by iatrogenic spread	12 (14%)	11 (12%)
Extracompartmental de novo	5 (6%)	9 (10%)
Tumour grade		
Low	15 (17%)	16 (17%)
Intermediate/high	73 (83%)	78 (83%)
Histological subtype		
Malignant fibrous histiocytoma	28 (32%)	23 (24%)
Liposarcoma	23 (26%)	26 (28%)
Leiomyosarcoma	9 (10%)	9 (10%)
Other histology	28 (32%)	36 (38%)
Anatomical site (limbs)		
Upper arm	10 (11%)	11 (12%)
Lower arm (include elbow)	8 (9%)	8 (9%)
Upper leg (include knee)	44 (50%)	54 (57%)
Lower leg	26 (30%)	21 (22%)
Tumour depth		
Superficial and deep to fascia	22 (25%)	28 (30%)
Deep to fascia	52 (59%)	46 (49%)
Superficial to fascia	14 (16%)	20 (21%)
Final resection margins		
Missing	1 (1%)	0
Negative on gross examination	14 (16%)	13 (14%)
Negative on gross and microscopic examination	73 (83%)	80 (85%)
Positive on both examinations	0	1 (1%)

Table 1: **Patients' and tumour characteristics of 182 patients evaluable for wound complications**

postoperative boost according to protocol. The other four did not receive the boost because of a wound complication (three), or because distant metastases developed before the boost could be given (one). Thus, of those evaluable for the primary endpoint, 74 of 88 patients who received preoperative radiotherapy received only the 50 Gy phase I protocol, with 14 receiving both phase I and phase II, whereas in the postoperative group 86 of 89 received the two-phase 66 Gy protocol. The median phase I field area was smaller in patients who had preoperative radiotherapy (333 cm^2, range 28–910) than in those who had postoperative treatment (416 cm^2, 84–1368; p=0·01).

More patients had wound complications in the preoperative radiotherapy group than in the postoperative radiotherapy group (difference 18% [95% CI 5–30], p=0·01; table 2), and risk of these complications varied according to anatomical site (table 3). The largest number of wound complications was seen in the thigh of patients in the preoperative group (table 3).

More patients given preoperative radiotherapy had non-primary wound closure (ie, wounds were closed with vascularised tissue transfer, or split thickness skin grafting, or both) than those in the postoperative group. But, the number of wound complications in the preoperative group did not differ between patients who had their wounds closed with primary techniques and those closed by non-primary methods (table 3).

Logistic regression for wound complications showed

	Preoperative (n=88)	Postoperative (n=94)
Wound complications*		
Yes	31 (35%)	16 (17%)
Secondary operation for wound repair	14 (45%)	5 (31%)
Invasive procedure for wound management†	5 (16%)	4 (25%)
Deep wound packing deep to dermis in area of wound at least 2 cm with or without prolonged dressings >6 weeks from wound breakdown‡	11 (35%)	7 (44%)
Readmission for wound care§	1 (3%)	0
No complications	57 (65%)	78 (83%)

*p=0·01 for yes *vs* no. †Without secondary operation. ‡Without secondary operation or invasive procedure. §Without secondary operation, invasive procedure, deep wound packing, or prolonged dressing.

Table 2: **Frequency of major wound complications with criteria for 182 evaluable patients**

that the significant variables were sequence of radiotherapy, maximum baseline tumour size, and anatomical site (upper and lower arms *vs* upper and lower legs) (table 4). The second logistic regression, which included variables that became available after randomisation, showed that preoperative radiotherapy (odds ratio 4·25, 95% CI 1·88–9·59), anatomical site (10·9, 1·39–85·0), and gross specimen size (substituted for maximum tumour dimension) (1·42, 1·16–1·73), were associated with wound complications. Wound reconstruction did not modify risk in this analysis. The final logistic model showed no treatment-by-covariate interaction, with p values for timing of radiotherapy (preoperative *vs* postoperative) by the different covariates as follows: anatomical site p=0·227; gross specimen size, p=0·319; type of wound reconstruction (primary *vs* non-primary closure), p=0·459. The overall interaction had a p of 0·242.

64 of 94 patients in the postoperative group had acute toxic skin effects that were grade 2 or greater, compared with 32 of 88 in the preoperative group (p<0·0001). Grade 1 and 2 toxic bowel effects did not differ between groups (six [7%] *vs* seven [7%], p=0·81) and was confined to hip and thigh lesions; no patient had grade 3 or 4 toxic bowel effects.

	Preoperative (n=88)	Postoperative (n=94)
Type of wound closure		
Primary	58 (66%)	72 (77%)
Vascularised tissue	25 (28%)	19 (20%)
Split skin graft	5 (6%)	3 (3%)
Wound complication by anatomical site		
Upper arm		
No	9 (90%)	11 (100%)
Yes	1 (10%)	0
Lower arm		
No	8 (100%)	8 (100%)
Yes	0	0
Upper leg		
No	24 (55%)	39 (72%)
Yes	20 (45%)	15 (28%)
Lower leg		
No	16 (62%)	20 (95%)
Yes	10 (38%)	1 (5%)
Wound complication by type of wound reconstruction		
Primary closure		
No	38 (66%)	58 (81%)
Yes	20 (34%)	14 (19%)
Non-primary closure		
No	19 (63%)	20 (91%)
Yes	11 (37%)	2 (9%)

Table 3: **Type of wound closure, and wound complications by anatomical site and wound reconstruction in evaluable patients**

	p step 0	p final	Odds ratio (95% CI)
Baseline variable			
Treatment (preoperative *vs* postoperative)	0·007	0·004	3·08 (1·43–6·64)
Maximum baseline tumour dimension (⩽10 cm *vs* >10 cm)	0·0001	0·0005	1·11 (1·05–1·18)
Anatomical site*	0·0004	0·0256	10·4 (1·33–81·1)
Age (years)	0·8204	0·8336	..
Sex (male *vs* female)	0·9562	0·7992	..
Healing detractors (yes *vs* no)*	0·9110	0·5256	..
Lesion type (locally recurrent *vs* first presentation)	0·0652	0·1054	..
Lesion type (already excised *vs* unresected)	0·2001	0·9262	..
Centre (other centre *vs* PMH)	0·8182	0·5639	..

PMH=Princess Margaret Hospital. *Covariate included the combined effect of these variables. *Upper and lower legs versus upper and lower arms.

Table 4: **Logistic regression for wound complications for baseline variables**

Patients given postoperative radiotherapy had greater function at 6 weeks after surgery than did those in the preoperative group. For patients in the postoperative and preoperative groups, respectively, the mean Musculoskeletal Tumor Society rating was 25 (SD 8) versus 21 (9) (p=0·01), the Toronto extremity salvage score was 69 versus 60 (p=0·01), and the short form-36 bodily pain score was 67 versus 58 (p=0·03). These function scores did not differ between treatment groups at later time points.

The local recurrence rate, the regional or distant failure rate, and progression-free survival did not differ between groups (figure 2). Overall survival was slightly higher in the preoperative group than in the postoperative group (figure 2). The two groups started to differ after 2·5 years of follow-up (figure 2). Table 5 shows the causes of death for patients in both groups.

Discussion

Our results show that the number of severe wound complications is related to timing of external-beam radiotherapy. The result confirms retrospective reports over the past decade, even though these reports could have been biased by selection of patients.[13–15] The finding is relevant to decision making in management of soft-tissue sarcoma because outcome, especially quality of life, is significantly associated with wound complication after limb conservation management for soft-tissue sarcoma.[25]

Two issues are important in the design of the trial. The first concerns the criteria for judging a wound complication. These criteria were developed empirically, mostly on the basis of observations by study investigators[14] and other knowledge from published work about assessment of wound complications.[7,13,14,16] Although some subjectivity might be present, most of the major complications arose in patients who needed a repeat

	Preoperative	Postoperative	Total
Status of patient at last contact*			
Alive	78 (85%)	68 (72%)	146 (78%)
Dead	14 (15%)	26 (28%)	40 (22%)
Cause of death			
Sarcoma	13 (93%)	21 (81%)	34 (85%)
Other†	0	3 (12%)	3 (8%)
Other primary malignant disease	1 (7%)	2 (8%)	3 (8%)

Values are number (%). *p=0·05 (alive *vs* dead). †Bronchopneumonia with 2-year follow-up without sarcoma; self-inflicted death without sarcoma with 3-year follow-up; fatal myocardial infarction near completion of postoperative radiotherapy.

Table 5: **Mortality and causes of death for all eligible patients**

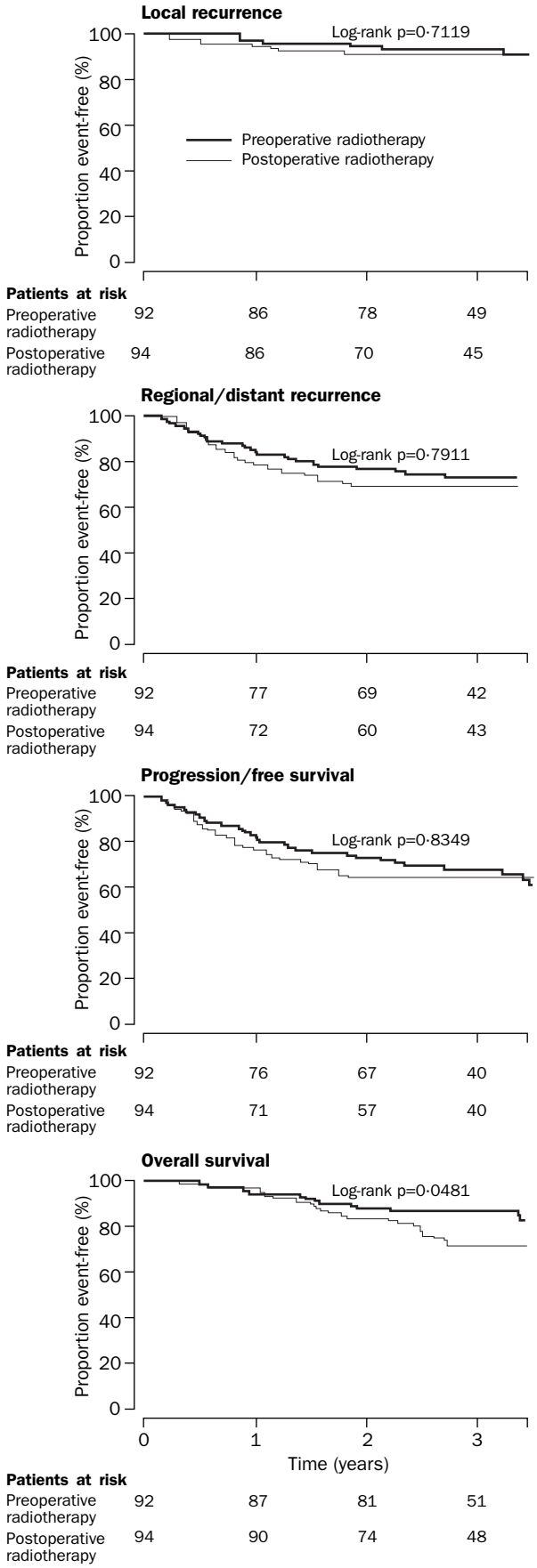

Figure 2: **Kaplan-Meier plots for probability of local recurrence, metastatic (regional and distant) recurrence, progression-free survival, and overall survival**

procedure for wound management or who had extended and invasive wound care (table 2).

The second issue relates to whether the type of wound closure (primary *vs* non-primary) might confound the outcome of the study. Thus bias towards non-primary wound reconstruction in the preoperative group might mask the preoperative radiotherapy effect on wound healing. Some surgeons seem to have elected to use vascularised tissue transfers for wound closure more frequently in patients receiving preoperative radiotherapy, despite the finding that tumour presentation did not differ between the two groups. Because vascularised tissue transfer would be expected to improve wound healing, the tendency to use non-primary wound closure in the preoperative radiation group might bias the study against the postoperative radiation group. However, the second exploratory logistic-regression analysis did not show an association between the type of wound closure and the risk of wound complications.

Although preoperative radiation is associated with a higher risk of wound complications than postoperative treatment, local anatomy should be considered when making recommendations about management of a specific patient. When dose and field size issues are the most important criteria, the preoperative approach might be preferable. This might apply to the arms, since this region of the body has a low risk of wound complication. Such an approach is especially relevant in the upper arm so that lung and joint tissues are protected, while also confining a significantly safer radiotherapy dose to an adjacent structure (eg, the brachial plexus in upper arm lesions). Preoperative radiotherapy also decreases acute toxic effects in the skin, although this self-limited toxic effect does not compare against the severity of most wound complications, which needed secondary wound repair in 14 of 88 preoperative patients compared with five of 94 postoperative patients (table 2).

Longer follow-up is needed to assess late manifestations of the larger-field, higher-dose approaches with postoperative radiotherapy compared with the more concise treatment volumes and lower dose associated with preoperative treatment. Although the preoperative radiotherapy protocol is detrimental to function in the early postoperative period (ie, at 6 weeks after surgery), function becomes comparable between treatment groups at subsequent assessment up to 1 year after surgery. We are continuing to gather data prospectively for physical function, limb oedema, and number of bone fractures. Such data could have implications for the best approach for specific patients, taking account of features such as the anatomical site and proximity to sensitive structures, the risk and consequence of complications, and the mode of wound reconstruction. That wound complications are significantly less frequent in patients who have with postoperative radiotherapy than in those who have preoperative radiotherapy does not reflect the complete nature of the clinical situation, which might be more complicated and could require a number of issues, including tumour size and anatomical site, to be considered for the individual patient.

The goal of combined surgery and radiotherapy in soft-tissue sarcoma is to achieve cure, and preserve function. To date, in this study, preoperative and postoperative approaches achieve similarly high levels of local control for extremity soft-tissue sarcoma, with no significant difference in progression-free survival rates. Although only a few randomised controlled trials have compared preoperative and postoperative radiotherapy in oncology, preoperative radiotherapy improves survival in patients with tumours at another site.[26] Nevertheless, at this time, the small survival benefit in favour of one group of our study must be interpreted with caution, since the excessive deaths in the postoperative group did not seem to be related to progression of the sarcoma alone. The conjecture that temporary presence of sarcoma cells in the peripheral blood circulation during surgery might add to metastatic spread[27] is of interest. However whether such wash-out of tumour cells during surgery is detrimental in sarcoma[28] and other tumour types[29,30] is not known, nor is whether preoperative treatments, including preoperative radiotherapy, could have a role in lowering the putative risk. Finally, the significance of the survival difference must itself be interpreted with caution since the study was not powered to detect a difference in this secondary endpoint and the timing of the survival analysis was not specified before the trial started.

The decision to accept increased short-term morbidity from wound healing complications must be balanced against potential effects of larger radiation doses and volumes associated with postoperative radiotherapy.

Contributors

All investigators contributed to the design of the study and writing of the report. B O'Sullivan, A Davis, and R Bell wrote the report. R Bell, B O'Sullivan, A Davis, and C Catton provided the conceptual basis. R Turcotte and P Chabot collaborated with these investigators to design the protocol. A Davis developed the TESS instrument with several members of the group. R Kandel did and coordinated the central pathology review. J Wunder and A Davis provided the prognostic variables used to describe the study sample, and, with R Bell and B O'Sullivan, developed the wound complication assessment criteria. C Catton and K Goddard did the real-time radiotherapy review and analysed the real-time radiotherapy review data. A Sadura, J Pater, and B Zee verified and analysed the data, and contributed to completion of the trial design.

Conflict of interest statement

None declared.

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