BJR

Received: 8 May 2013 | Revised: 21 May 2013 | Accepted: 22 May 2013

doi: 10.1259/bjr.20130258

Cite this article as:
Soyfer V, Corn BW, Kollender Y, Issakov J, Dadia S, Flusser G, et al. Hypofractionated adjuvant radiation therapy of soft-tissue sarcoma achieves excellent results in elderly patients. Br J Radiol 2013;86:20130258.

FULL PAPER

Hypofractionated adjuvant radiation therapy of soft-tissue sarcoma achieves excellent results in elderly patients

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Objective: Adjuvant radiation therapy (RT) is an essential part of combined limb-sparing treatment of soft-tissue sarcoma (STS). Elderly or medically unfit patients often have difficulty in completing 6–7 weeks of standard fractionated daily treatment. Our aim was to evaluate the efficacy of a hypofractionated adjuvant approach with RT for STS in elderly and debilitated patients.
Methods: 21 elderly patients were treated with a short course of adjuvant RT (39–48 Gy, 3 Gy per fraction) for STS. The medical records of the patients were retrospectively reviewed for local or distant recurrence and side effects of RT.
Results: At a mean 26 months of follow-up, three local recurrences (14%) were detected. Eight patients (38%) had lung metastases during the observed period. Three of them died from metastatic disease. The hypofractionated radiation was well tolerated with minimum long-term side effects.
Conclusion: Hypofractionated adjuvant radiation appears to be an effective treatment in terms of local control in elderly and debilitated patients.
Advances in knowledge: The results of this study might provide an alternative to commonly used standard fractionation of radiotherapy in sarcoma patients.

Soft-tissue sarcoma (STS) is a relatively rare disease. The age-adjusted incidence rate is 3.3 per 100 000 males and females per year. From 2005 to 2009, the median age at diagnosis for cancers of the soft tissue was 58 years. Approximately 16.1% were diagnosed between 65 and 74, 16.3% between 75 and 84 and 7.3% at 85+ years old [1].

The modern approach to high-grade limb STS in adults is based on limb-sparing surgery followed by radiation therapy (RT). The benefit of RT in terms of local control was documented in two randomised trials [2,3]. The indications for pre-operative or post-operative chemotherapy are not sufficiently clear at this juncture. Adjuvant RT is an essential part of combined limb-sparing treatment of STS. The recommended dose of radiation lies in the range of 60 Gy in standard fractionation of 1.8–2.0 Gy. Elderly or medically unfit patients often have difficulty in completing 6–7 weeks of daily treatment. Moreover, a prolonged course of radiation may be interrupted by acute side effects, which sometimes demands further extension of the overall course or even discontinuation of treatment.

We retrospectively studied the rate of local control and distant metastases in elderly patients with STS treated by short-course adjuvant radiation.

PATIENTS AND METHODS

The patients' characteristics are presented in Table 1. 21 elderly or medically unfit patients diagnosed with STS were treated by RT following curative surgery. There were 13 males and 8 females. The median age was 80 years. The most common comorbidities were hypertension, diabetes mellitus and cognitive disorders (Table 1). The decision to treat patients with a hypofractionated regimen was based on the clinical assessment by physicians. Inclusion criteria included functional performance status >0 (Eastern Co-operative Oncology Group scale), large distance from the medical centre or a patient's desire to receive the short course of treatment as an alternative to the conventional/longer course that they refused to accept. The types of sarcoma included malignant fibrohistiocytoma (two), liposarcoma (two), leiomyosarcoma (three), pleomorphic sarcoma (seven), fibrosarcoma (six) and synovial sarcoma (one). The anatomical distribution of the primary tumours were thigh (seven), calf (five), arm (four), shoulder (two) and pelvis (one). Most of the patients underwent marginal excision of tumour (17). No widening of surgical margins was attempted owing to the general condition of the patients. In 15 patients, the surgical margins were <5 mm, 4 of them were involved by microscopic disease.

Table 1. Patients' demographics and tumour characteristics

No.	Gender	Age (years)	PS	Comorbidity	Site	Type STS	Size (cm)	Type of surgery	Margins	Days before start of radiation therapy
1	M	90	1	HTN, BPH, LHR	L calf	MFH	3.5	WLE	0.4 cm	108
2	F	82	1	HTN, BPH, LHR	R thigh	WDLS	10.0	Marginal (sk graft)	Positive	69
3	F	68	1	Cardiac myxoma	R thigh	Rec LMS	8.0	Marginal	1.0 mm	74
4	M	76	1	HTN, CRF, BPH	L arm	Pleom HG	19.0	Marginal	Positive	42
5	M	80	1	COPD	L arm	MFH	16.0	Marginal	2.0 mm	48
6	M	86	0	IHD, NIDDM	L arm	MyxoFS	5.0	WLE	2.5 cm	83
7	M	75	2	HTN, IHD	L pelv	MyxoFS	20.0	Marginal	2.0 mm	90
8	F	76	1	HTN, NIDDM, Alzheimer	L thigh	LS	4.5	Marginal	4.0 mm	70
9	M	87	2	Gout	R shoulder	Rec Pleom HG	2.3	Marginal	2.0 mm	48
10	M	85	2	HTN, CVA	L calf	LMS	8.0	Marginal (sk graft)	3.0 mm	67
11	F	89	2	COPD, Ca of uterus	R knee	Rec FS	8.0	Marginal (sk graft)	3.0 mm	50
12	M	87	1	NHL, IHD	R thigh	Pleom HG	19.0	Marginal	1.0 mm	42
13	M	66	3		L arm	LMS	1.5	WLE	1.0 cm	90
14	M	86	2	HTN, BPH, LHR	L thigh	FS	30.0	WLE	1.0 cm	61
15	M	56	1	HIV, low compliance	L shoulder	SS	14.0	Marginal	Positive	57
16	M	80	1	HTN, BPH, AF, Parkinson	L calf	Pleom HG	6.0	Marginal	?	20
17	F	78	2	Bipolar ds, Ca of breast	L thigh	Pleom HG	7.0×5.0×2.0	Marginal	1.0 mm	62
18	F	89	1	HTN, IHD, COPD, goitre	R forearm	FS	8.0×5.0×5.0	Marginal	1.0 mm	74
19	M	86	1	IHD, CRF, CHF, Pulm HTN	R thigh	Pleom HG	10.0×5.0×4.0	Marginal	2.0 mm	63
20	F	76	1	HTN, DM, CRF	R calf	MyxoFS	2.5 cm	Marginal	5.0 mm	46
21	F	80	2	Peptic ds, OA	L calf	Pleom HG	12.0×7.0×6.0	Marginal	Positive	102

AF, atrial fibrillation; BPH, benign prostatic hyperplasia; Ca, cancer; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVA, cerebral vascular accident; DM, diabetes mellitus; ds, disorder; F, female; FS, fibrosarcoma; HG, high grade; HIV, human immunodeficiency virus; HTN, hypertension; IHD, ischemic heart disease; L, left; LHR, left hip replacement; LMS, leiomyosarcoma; LS, liposarcoma; M, male; MFH, malignant fibrous histiocytoma, MyxoFS, mixoid fibrosarcoma; NHL, non-Hodgkin lymphoma; NIDDM, non-insulin dependant diabetes mellitus; No., number; OA, osteoarthritis; Pulm, pulmonary; PS, performance status; R, right; sk, skin; SS, synovial sarcoma; STS, soft-tissue sarcoma; WDLS, well-differentiated liposarcoma; WLE, wide local excision.

Most tumours had a high-grade malignancy (Grades 3–17) and were >5 cm in size (16), with 8 of them >10 cm.

All patients underwent CT simulation (Brilliance Big Bore; Philips, Best, Netherlands). The positioning and immobilisation of patients was individualised as a function of tumour location. Beams were designed to achieve coverage of the clinical treatment volume (CTV) based on the pre-operative CT scan or MRI and clips that surgeons placed at the tumour bed and its edges. Traditionally, the borders of the CTV were arranged in extension of 2–5 cm beyond the pre-operative tumour volume depending on the margin status. Treatment planning was carried out with the XiO® system (CMS Corporation, St. Louis, MO) and was consonant with requirements of the International Commission on Radiation Units & Measurements report 50 [4]. Before the start of treatment, each patient had verification of portals (I-View™ GT-IVIEW02; Eleka, Crawley, UK). The radiation was administered with Elekta (Stockholm, Sweden) linear accelerators with energies of 6 MV or 18 MV. Patients were assessed for side effects and compliance with treatment on a weekly basis during therapy: at the end of treatment, and every 3 months thereafter. All patients were treated by a short and intensive course of therapy: 39 Gy was given in 13 fractions of 3 Gy day^{-1}, 5 times a week to patients with closest surgical margins of at least 5 mm, whereas a dose of 48 Gy given in 16 fractions was provided in cases of margins that were closer than 5 mm.

The patients were scheduled for follow-up according to European Society for Medical Oncology guidelines [5] for regular physical examination every 3–4 months after completion of RT in addition to semi-annual MRI or CT scans of the treated site and CT scanning of the chest. The date of local recurrence or first distant metastases was registered for calculation of the disease-free progression and the rate of local control.

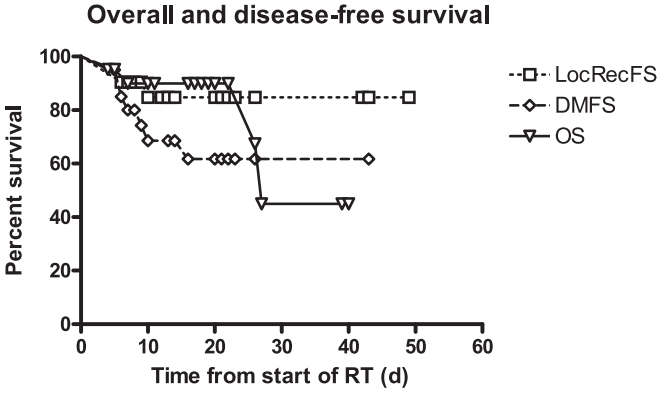
RESULTS

Overall, the hypofractionated irradiation regimen of 39–48 Gy in 13–16 fractions was well tolerated with only 3 patients developing Grade 2 or 3 acute toxicity (mainly dermatitis). Three patients had delayed Grade 2 or 3 toxicity (chronic pain, skin atrophy, telangiectasia) scaled according to common toxicity criteria [6].

The mean time from surgery until the initiation of RT was 2.1 months [standard deviation (SD) 0.7]. Mean radiation treatment time was 18.4 days (SD 3). No delay in treatment owing to acute toxicity was registered. All patients except for one were able to receive RT in the ambulatory setting.

With a mean follow-up of 26 months (SD 10.7), three local recurrences (14%) were detected (all in patients with surgical margins <3 mm). Three of eight patients with distant metastases died of sarcoma (Figure 1). One patient with metastatic disease in the lung received salvage stereotactic RT and was still alive 6 months after completion of stereotactic body radiotherapy with no evidence of disease. The Kaplan Meier curves for overall and disease-free survival were plotted, and the results were similar to those of soft-tissue sarcoma patients treated with standard fractionation (Figure 1).

Figure 1. Overall and disease-free survival of patients with soft-tissue sarcoma treated by hypofractionated radiation therapy. DMFS, distant metastases free survival; LocRecFS, local regional free survival; OS, overall survival; RT, radiotherapy.



DISCUSSION

Our data point to the feasibility, safety and efficacy of adjuvant hypofractionated RT following limb-sparing surgery in adults with high-grade STS of the limb. The local control rate was 86%, which is similar to results of usually recommended adjuvant treatment in standard 1.8–2.0-Gy fractionation [7].

The hypofractionated treatment seems to be especially suitable for elderly patients with significant comorbidities. None of the patients interrupted treatment owing to underlying diseases or poor compliance.

In view of their age and underlying medical condition, the patients in the current study represent a cohort with undesirable risk factors in relation to expected compliance and tolerability. Most of them refused the proposed standard 6–7-week course of adjuvant RT owing to complicated logistics or comorbidities. Our results show good tolerability and acceptable 2-year local control with the short course of adjuvant RT among debilitated or elderly patients with STS.

A shorter course of RT is much easier for patients and for accompanying family members or caregivers. In the presence of acceptable efficacy and tolerability, a shorter course of RT may also be economically justified.

In a recent report from the Memorial Sloan–Kettering Cancer Center, the 5-year local recurrence rate was 9%. Old age and stage 3 disease were identified as factors associated with a higher rate of local recurrence [8].

From a radiobiological perspective, sarcomas are usually considered as poorly to moderately radioresponsive tumours. RT doses in the range of 60–70 Gy are usually necessary in order to eradicate microscopic disease. One of the biological characteristics of sarcoma cells is their relatively low (−0.5 to 5.4) α–β ratio [9]. This ratio, theoretically, may justify the use of larger-than-standard fractionation in order to achieve significant cell kill by RT.

Assuming an α–β ratio of sarcoma cells of 4, our calculation of the equivalent dose in 2-Gy fractions (EQD2) resulted in 46 Gy and

56 Gy, respectively, for 13 and 16 fractions of 3 Gy using the formula of EQD2=$D[d+\alpha/\beta]/[2+\alpha/\beta]$ [9]. In cases of margins closer than 5 mm or frankly positive margins, we augmented the dose to 48 Gy in 16 fractions. Moreover, the use of hypofractionation in adjuvant RT is becoming widely adopted in the treatment of different solid tumours [10,11]. The historical assumption that standard fractionation of 1.8–2.0 Gy is acceptable for most malignant tumours is therefore being re-assessed by many clinical investigators.

In our previous publication [12], we reported good tolerance and high efficacy of the same hypofractionated regimen among patients with metastatic STS in terms of local control for macroscopic disease.

Eilber et al [13] first applied a hypofractionation regimen for treatment of STS.

Ryan et al [14] achieved a high rate of pathological tumour necrosis (95%) following 28 Gy administered in eight fractions. We found these regimens to be intriguing and worthy of further study.

We previously reported good tolerance and results with a short course of palliative radiation delivered to unfit patients with STSs. This prompted us to consider applying a similar regimen in the adjuvant setting. This new option is worthy of consideration for a challenging population (*i.e.* elderly/medically unfit) for whom some would contemplate foregoing irradiation despite the consensus that RT is a critical therapeutic component [3,7]. Omitting RT in a patient treated with limb-sparing surgery increases the risk of local recurrence [7]. As an alternative to limb-sparing surgery without RT, amputation surgery may be suggested, hampering the quality of life even more, and possibly rendering the patient bed-ridden. A short and intensive course of RT may be a logical and adequate solution to this dilemma.

An interesting dimension of our study was the ability to achieve high rates of local control despite a surgical policy that did not insist on attaining negative margins. This is particularly noteworthy in light of the emphasis on the importance of margin status by McKee et al [15]. At the same time, it is intriguing that the previous emphasis on the importance of margin status is being revisited throughout oncology [16]. Whether the use of hypofractionated regimes such as the one employed at our institution can overcome the significance of involved or close margins is worthy of further study.

The limitations of the current study are the small number of patients and the relatively short observation time. Since our conclusions are not attributable to a database of prospectively randomised patients, our findings are only hypothesis generating. Notwithstanding, the promising results might provide insight into revision of the standard fractionation used in the field of soft-tissue malignancy.

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