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ScienceDirect

EJSO 40 (2014) 394–401

EJSO the Journal of Cancer Surgery

www.ejso.com

Tumour volume changes following pre-operative radiotherapy in borderline resectable limb and trunk soft tissue sarcoma

F. le Grange [a,*], A.M. Cassoni [a], B.M. Seddon [a,b]

[a] University College London Hospitals NHS Foundation Trust, Department of Oncology, 1st Floor Central, 250 Euston Road, London NW1 2PG, UK

[b] NIHR University College London Hospitals Biomedical Research Centre, 1st Floor Maple House, Suite A, 149 Tottenham Court Road, London W1T 7DN, UK

Accepted 17 January 2014

Available online 2 February 2014

Abstract

Aims: To evaluate tumour volume changes after preoperative radiotherapy (PRT) for borderline operable soft tissue sarcomas (STS).

Materials and methods: A retrospective review was performed of 68 patients who received PRT between December 2004 and July 2011. Endpoints were radiological response, surgical margins, local control and survival.

Results: Median tumour size was 12.5 cm. Tumour location was extremity (87%), trunk (12%), and neck (1%). Commonest histological subtypes were myxoid liposarcoma (32%) and myxofibrosarcoma (16%). The majority of patients (88%) received 50 Gy in 25 fractions. Post-radiotherapy imaging was available in 55 cases. By RECIST there was stable disease in 89%, partial response in 7% and progressive disease in 4%. Tumour volumes reduced in 80%. Median change in maximal tumour dimension was −13.6%; median change in volume was greater, at −33.3%. Tumour volumes increased in 11 cases (20%). However, surgical margins were clear in all 11 cases, with no local recurrences in this group. For the entire group, surgical margins were clear in 93%, and microscopically positive in 7%. Eight patients (12%) had local relapse at 2–24.8 months after surgery. Two year local relapse free survival was 87.5%; 2 year overall survival was 74.7%.

Conclusion: The majority of tumours showed reduction in volume. A small number of tumours increased in volume, but there was no definite relationship between volume increase and poor surgical outcomes or lower local control rates. Local control was equivalent to published series' of PRT. PRT is a reasonable approach in patients with borderline resectable tumours.

Keywords: Local control; Pre-operative; Radiotherapy; Soft tissue sarcoma; Surgical margins

Introduction

Current multi-modality treatment of localised soft tissue sarcomas (STS) is aimed at achieving long-term local tumour control and cure, maximising function, and minimising treatment related morbidity. Prognostic factors predicting disease-specific survival include size, site, grade, histological subtype, age, and the completeness of the surgical resection margins.[1] The aim of surgery is therefore to achieve clear resection margins with as wide margins as feasible, aiming for optimal functional outcome, especially where the tumour may be close to neuro-vascular structures, joints and bone. Limb-sparing surgery with adjuvant radiotherapy achieves similar overall survival rates to amputation in STS of the extremities and is now the preferred approach.[2] Local control rates of more than 80% have been reported in published series' and a large systematic review.[1,3–6] There is currently no consensus on the ideal timing for adjuvant radiotherapy, which may be given either before or after surgery.[7–10] Furthermore, there are other neo-adjuvant approaches in the local management of soft tissue sarcomas that include chemotherapy, chemo-radiation, and isolated limb perfusion, particularly for high risk tumours of borderline resectability.[11–13]

Comparisons of pre-operative (PRT) and post-operative radiotherapy indicate at least equivalent outcomes for local control rates and overall survival.[7,9,10] However, PRT offers

* Corresponding author. Tel.: +44 20 3447 9866; fax: +44 20 3447 9055.

E-mail address: franel.legrange@uclh.nhs.uk (F. le Grange).

0748-7983/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2014.01.011

potential advantages of reduced late toxicity and improved functional outcomes, while maintaining good local control rates.[14] This is by virtue of smaller normal tissue volumes treated to lower doses than with post-operative radiotherapy[15,16] In addition, PRT may improve resection margins in borderline resectable tumours, as it may improve resectability by making the tumour easier to handle at surgery, thereby reducing the risk of tumour rupture and tumour bed contamination. In addition, it may cause tumour shrinkage, thereby facilitating microscopic complete resection.[3]

Our current unit practice is to offer post-operative radiotherapy as standard adjuvant treatment for patients with high risk adult-type STS. PRT with or without neo-adjuvant chemotherapy is recommended in patients with tumours of borderline operability in an attempt to improve the chances of complete resection. In recent years we have moved to offering PRT to the majority of patients with myxoid liposarcomas, as this histological subtype is expected to respond well to radiotherapy. However, patients in the current series with myxoid liposarcoma all had tumours of borderline resectability.

In order to better understand the role of pre-operative radiotherapy as neo-adjuvant treatment in soft tissue sarcoma of borderline resectability, we retrospectively reviewed our unit experience, with particular reference to changes in tumour volume, how these relate to more conventional linear response assessment with RECIST, and whether volume changes predict long term local tumour control.

Materials and methods

A retrospective review of patient records was performed of adult patients with STS treated within the London Sarcoma Service at University College Hospital with a course of PRT between December 2004 and July 2011. Minimum follow-up after completing treatment was 6 months. Patients who received neo-adjuvant chemotherapy were excluded to avoid bias when assessing changes in volume after treatment. One patient who had clear disease progression after 1 cycle of neo-adjuvant chemotherapy, and one patient who had no evidence of response and declined further chemotherapy after 2 cycles, were included. We aimed to describe volume change after radiotherapy in adult-type soft tissue sarcoma only. Paediatric-type tumours (alveolar and embryonal rhabdomyosarcoma, primitive neuro-ectodermal tumours and extra-osseous Ewing's sarcoma family of tumours) have been excluded as radiotherapy dose, techniques and expected response after treatment are different to adult-type soft tissue sarcoma.

All cases were discussed in the London Sarcoma Service multi-disciplinary team meeting with radiology and pathology review. Patients deemed to have borderline resectable tumours were recommended to have PRT. The standard prescription dose was 50 Gy in 25 daily fractions, 5 days per week. Patients underwent MRI scanning prior to radiotherapy, which was repeated approximately two weeks prior to surgery. Surgery (aiming for wide local excision) was performed approximately 6 weeks after completion of radiotherapy. Information on surgical resection margins and histological response to radiotherapy were taken from the pathology reports. Margins were classified as a microscopically complete (R0), microscopically positive (R1), or macroscopically positive (residual tumour, R2).

Radiological change on MRI scans was defined as a decrease in size or change in signal on the post-radiotherapy, pre-surgery imaging. Information on signal change within the tumour was obtained retrospectively from radiology reports and documented MDT discussions. Change in size was assessed according to response evaluation criteria in solid tumours (RECIST),[17] as well as on comparison of three dimensional tumour volumes. Pre-treatment tumour volume was calculated from the gross tumour volume (GTV) as outlined on the radiotherapy planning CT scan guided by the baseline diagnostic MR imaging. The post-radiotherapy tumour volume was outlined and calculated on the diagnostic imaging following PRT, using Oncentra MasterPlan® version 3.2 (Nucletron).

Outcome measures and statistical analysis

Data were analysed using Microsoft Excel (2010) and R version 2.14.1 (2011).[18] Patient follow-up and survival were measured from the date of surgery. Local recurrence free survival and overall survival were calculated using the Kaplan–Meier method taking censored data into account. Correlation was calculated using Spearman's rank correlation coefficient.

Results

Patient characteristics and treatment

Sixty-eight patients were studied, with a median follow-up of 35.2 months (range 0–61.7months) (Table 1). The median age of the group was 54 years (range 13–87 years). The majority (87%) of tumours were located in the extremities, most frequently in the lower limb (71%). The median tumour size was 12.5 cm (range 3.5–33 cm). Most tumours (66, 97%) were located deep to the fascia, and all were grade 2 or 3. The most common subtype was myxoid liposarcoma (32%) followed by myxofibrosarcoma (16%). Sixty-seven cases were primary presentation, with only one case treated as a local recurrence.

Sixty patients (88%) received 50 Gy in 25 daily fractions over five weeks. The remaining eight patients received doses ranging from 44 Gy to 50.4 Gy in 22–28 daily fractions, at clinician discretion. Three patients with microscopic positive (R1) surgical margins received a post-operative radiotherapy boost, of 16 Gy in 8 daily fractions (two patients), and 9.96 Gy in 6 daily fractions (one patient).

All patients underwent surgical excision at a median of 7 (range 3–16) weeks after completing radiotherapy. Fifty-