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ScienceDirect

EJSO 40 (2014) 1648–1654

EJSO the Journal of Cancer Surgery

www.ejso.com

Is preoperative radiotherapy suitable for all patients with primary soft tissue sarcoma of the limbs?

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Accepted 30 June 2014
Available online 25 July 2014

Abstract

Aim: To evaluate the indications and results of preoperative radiotherapy (RT) on a series of selected patients treated at our institution with curative intent for a limb sarcoma (STS).
Patients and methods: From 05/1993 to 12/2011, 64 STS patients received preoperative RT.
Results: RT was delivered as a "limb salvage treatment" prior to surgery for the following reasons: as the preferential induction treatment in 53 patients (83%) or as a second intent (17%) after the failure of neoadjuvant systemic chemotherapy/isolated limb perfusion. Surgery was performed after RT in 54 (84%) patients and final limb salvage was performed in 98%. Musculo-cutaneous flap reconstruction was planned upfront in 44% patients, and 19% had a skin graft. Seven patients (13%) had a postoperative RT boost. Thirteen (20%) patients had grade (G) 3/4 adverse events, one after RT and 12 after surgery. At a median follow-up of 3.5 years, the 3-year actuarial overall survival (OS) and distant relapse (DR) rates were 83% and 31%, respectively. Two patients developed a local relapse and two a local progression (non-operated patients). In the multivariate analysis (MVA), histological subtype (leiomyosarcoma) and grade 3 were predictive of poorer survival. Patients with >3 month delay between the start of RT and surgery at our institution had an increased risk of DR in the MVA.
Conclusion: Induction RT should be personalised according to histological subtype, tumour site and risks-benefit ratio of preoperative radiotherapy and is best managed by a multidisciplinary surgical and oncology team in a specialist sarcoma centre.

Keywords: Preoperative radiotherapy; Surgery; Limb sarcomas; Extremities; Chemotherapy; Prognosis

Introduction

Preoperative vs. postoperative radiotherapy (RT) in sarcomas of the extremities has been a controversial issue for years and has been addressed by one randomised trial[1] and a systematic overview.[2] Outcomes in terms of local control and survival seem equivalent, but the risk of postoperative complications is higher if RT is administered before surgery. Thus, as with other neo-adjuvant treatments such as chemotherapy or isolated limb perfusion (ILP), preoperative radiotherapy should always be discussed upfront within a multidisciplinary team.[3] There are indeed pros and cons of both preoperative and postoperative radiotherapy. In the case of no neo-adjuvant treatment, the pathologist can easily evaluate the grade of the tumour (which remains

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http://dx.doi.org/10.1016/j.ejso.2014.06.014
0748-7983/

the main prognostic factor since the initial percutaneous biopsy may underscore this grade), tumour size and the precise histological evaluation of margins. With preoperative RT, tumour volume is easier to delineate for accurate treatment planning; in addition, the treatment volume is smaller, as there is no need to include the whole scar, and biologically effective radiation dose is possibly lower. Several retrospective studies have shown similar local control and specific survival rates between the two strategies.[2,4,5] In the only phase III clinical trial addressing this question, O'Sullivan et al. reported that the 94 patients assigned to preoperative RT (50 Gy+-postoperative boost of 16–20 Gy in case of positive margins) had more acute wound complications (35 vs. 17%; $p = 0.01$; median follow-up: 3.3 years) than the postoperative group ($n = 88$; 66 Gy to the initial field).[1] However, in the latest update (median follow-up: 6.9 years), there was no difference in terms of survival or local, regional, and distant failure rates. Moreover, postoperative RT patients had more severe late toxicity than those treated preoperatively (severe induration, loss of subcutaneous tissue, subcutaneous fibrosis).[6,7] Therefore, it is important to define optimal indications of preoperative radiotherapy. In this study, we aimed to evaluate the indications and results of preoperative RT on a series of patients treated at our institution with curative intent for limb sarcoma.

Methods

Study outline and definitions

Data were collected on 607 consecutive patients with primary limb sarcoma who were treated by the same team at Gustave Roussy, France, from 05/1993 to 12/2011. Patients with pelvic ($n = 7$), regional ($n = 4$), or metastatic ($n = 28$) initial extension were excluded from our analysis, as well as patients who had no preoperative RT ($n = 484$), treatment process outside of our institution only ($n = 16$), and no curative local treatment ($n = 4$). Thus, 64 patients treated between 04/1999 and 10/2011 were considered eligible for our study. The 2010 American Joint Committee on Cancer (AJCC) 7th edition was used for staging.[8] The diagnosis was centrally confirmed by a specialised pathologist (PT). Tumour types were characterised following the criteria defined by Enzinger and Weiss[9] and graded according to the French system.[10] Tumour satellites within 2 cm were considered multifocal localised disease and were rated according to the largest nodule diameter. All magnetic resonance imaging (MRI) exams were reviewed by a single radiologist. Radiological tumour response was assessed on T1 gadolinium enhanced MRI according to RECIST 1.1. The status of the resection margins in surgically treated patients was classified according to the UICC "R" classification.[11] Patients were followed with MRI and chest computed tomography every 6 months for 5 years and then yearly.

Toxicities

Patients were evaluated by chart review using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4) for acute toxicity and the Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scales (LENT SOMA) for late toxicity.

Statistical analysis

Follow-up was estimated using the reverse Kaplan–Meier method. Overall survival (OS), progression-free survival (PFS), specific survival (SS), local relapse (LR), and distant relapse (DR) rates were estimated using the Kaplan–Meier method. Survival rates were defined as the time between the date of pathological diagnosis and the first event. Events were death from any cause for OS, death or tumour progression for PFS, and death from the treated cancer or after a relapse for cause-specific survival. For the LR and DR rates, death without relapse or a relapse other than the one considered was censored. Survival curves were compared using the log-rank test for univariate analyses and a multivariate ascending stepwise Cox regression for multivariate analyses. In the Cox model, continuous variables (age, tumour size, and delays) were dichotomised. Statistical analyses were performed using SPSS software, version 19 (SPSS Inc., United States). All reported p values are two sided, and p values less than 0.05 were considered significant.

Results

Patients

According to our centre policy, RT was delivered prior to surgery for the following reasons: as the preferential induction treatment for large sarcomas as "limb salvage treatment" in 53 patients (83%) (myxoid liposarcomas: $n = 8$ [13%], high grade tumour in patients over 60: $n = 16$ [25%], locally advanced proximal [$n = 20$; 31%] or distal [$n = 8$; 13%], and low grade tumour in a patient <55 years: $n = 1$) or after failure of neoadjuvant systemic chemotherapy/ILP ($n = 11$; 17%). In our study, the proximal location corresponded to the upper third of the thigh or the arm; patients with proximal sarcomas were not eligible for ILP.

Pathological diagnoses were obtained with a biopsy in 48 cases (75%; $n = 13$ surgical and $n = 35$ percutaneous biopsy) or after incomplete excision outside our institution in 16 cases (25%). Baseline patient and tumour characteristics are shown in Table 1. The median age was 62 years (range: 16–87 years). The median tumour size was 8.7 cm (range: 1.7–23 cm). The most frequent locations were deep to fascia (84%), on the lateral side (58%), and on the thigh (48%). The most frequent subtypes were liposarcoma ($n = 18$; 28%), leiomyosarcoma ($n = 16$; 25%),