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Original article

Is dose de-escalation possible in sarcoma patients treated with enlarged limb sparing resection?

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ABSTRACT

Purpose: To evaluate the impact of dose de-escalation in a large series of resected limbs soft tissue sarcomas (STS).

Methods: Data were retrospectively analysed from 414 consecutive patients treated for limb STS by enlarged surgery and radiotherapy at Gustave Roussy from 05/1993 to 05/2012. Radiotherapy (RT) dose level was decided by the multidisciplinary staff and depended upon the quality of surgery and margins size.

Results: RT was delivered prior (13%) or after (87%) surgery. Seven patients (2%) had pre- and a postoperative RT boost. Median delivered RT dose was 50 Gy (36–70 Gy), and 33% received ≥55 Gy. At a median follow-up of 6.8 years, the 5-year actuarial local relapse (LR) rate was 7% (95% CI: 4.4–10%). The median time to the first LR was 2.7 years (range: 0.6–11.2 years). The LR was most often located within the irradiated field (26/32; 81%), where the median total applied dose was 56 Gy (range, 40–60 Gy). The 5-year LR rates were 4%, and 15% in patients receiving <55 Gy, and in those who had ≥55 Gy ($p < 0.001$), respectively. In the multivariate analysis, dose ≥55 Gy (HR [hazard ratio]: 2.9; $p = 0.02$), certain histological subtypes (HR: 7.8; $p < 0.001$), and minimal surgical margins <1 mm (HR: 2.9; $p = 0.02$) were associated to higher LR rates. In the subgroup of patients with "positive" margins <1 mm ($n = 102$), these histological subtypes (HR: 4.4; $p = 0.03$), and inadequate initial surgery justifying re-excision (HR: 3; $p = 0.048$) predicted for an increased LR, whereas dose of irradiation did not ($p = 0.2$). Patients who had late complications ($n = 64$; 15%) received higher doses of irradiation as compared with other patients (median: 55 Gy vs. 50 Gy, respectively; $p < 0.001$).

Conclusion: In this retrospective analysis of patients having enlarged surgery and RT, histological subtype is the strongest predictor of LR, whereas dose de-escalation did not lead to worse outcomes. A dose of 50 Gy may be recommended in case of planned enlarged surgery with R0 margins.

Extremity soft tissue sarcomas (ESTS) display a large variety of histology subtypes [1] and account for approximately 50% of all soft tissue sarcomas [2]. Adjuvant radiotherapy (RT) is a standard procedure in patients considered at risk of local recurrence as it improved local control (LC) in 2 randomized studies [3,4]. In the past decades, efforts have been made to set up the optimal radiation dose/fractionation regimen in this setting. Contradictory results regarding sarcoma radiosensitivity have been reported in preclinical models [5,6], and alternative fractionation schedules have been disappointing [7]. With respect to limb function, conformal preoperative RT at moderate dose levels (50 Gy [Gray] to the tumour bed in 5 fractions of 2 Gy weekly) is traditionally prescribed, whereas higher doses are generally prescribed in the postoperative setting [8,9]. As the status of surgical margins is one of the most important treatment variables that adversely influence LC [10,11], some authors have advocated that adjuvant RT at higher doses could improve the outcome in patients with positive margins [12]. Additional postoperative boost of 10–16 Gy is then generally delivered in case of positive surgical margins, but this remains controversial. Recent series in a limited number of patients reported similar LC after a postoperative boost in ESTS patients receiving preoperative RT, and a potential greater risk for late complications [13,14]. We then aimed to evaluate if multimodal management including irradiation delivered at a total dose modulated according to the risk of local recurrence could decrease this risk in a large series of ESTS patients.

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Patients and methods

Study outline and definitions

Data were retrospectively analysed from consecutive localized ESTS patients who received conformal radiation therapy and enlarged surgery at Gustave Roussy from 05/1993 to 05/2012. Patients who did not receive surgery within our institution, who did not receive radiotherapy, who were admitted for a local relapse (LR), or who had metastases at diagnosis were excluded. Thus, 414 patients were considered eligible for our study. The diagnosis was centrally confirmed by a specialized pathologist (PT), and all of the patients were operated upon by a single surgeon (SB). The tumour types were characterized following the World Health Organization criteria and graded according to the French Federation of Cancer Centers system. The margins were assessed on the pathological specimen after fixation in formalin and ink-dying of the surface [15]. The margins were classified according to the Union for International Cancer Control (UICC) "R" classification: a R1 resection was characterized by the presence of tumour at the inked surface. The minimum margin was prospectively registered and defined both in terms of length (mm) (0 mm in R1 resection, X mm in R0 resections) and the constituting tissue (i.e., fascia, fat, muscle). In the group of patients who received neoadjuvant treatment, the cut-off to differentiate responders was defined as <10% of remaining tumour cells [15]. In all R1 patients, re-excision would be discussed. In case of re-excision with no residual tumour found, a dose of 50 Gy was administered to the Planning Target Volume (PTV) including the surgical scar and surgical drain site. In case of R1 excision after preoperative RT, a postoperative boost was discussed and administered only in patients considered at high risk of recurrence because of multiple R1 zones.

RT dose level was discussed at multidisciplinary staff and depended mostly upon the quality of surgery, margin size and type of tissue, as well as timing of RT. Histotype, patient's age as well as consequences of a possible local recurrence could be considered in the decision. Three-dimensional conformal RT planning generally included modern procedures with immobilization device and in the last years, the target volume was based on the fused preoperative magnetic resonance imaging (MRI). Target volume recommendations were previously described [9]. As traditionally required, drain sites and the surgical scar were included in the clinical target volume (CTV), which covered 1 cm beyond the scar, so that there was a longitudinal margin of 2–3 cm craniocaudal and 1–1.5 cm radial (with exclusion of bone or fascial barriers) beyond the gross tumour. PTV expansion was generally 5–10 mm, and >95 percent of the dose was delivered to the PTV. A boost to the tumour bed with a 1.5 margin would be administered to bring the tumour bed to a dose of 60–66 Gy depending on margins status. Of note, patients who had isolated limb perfusion (ILP) received 45 Gy in 25 fractions, so as to minimize possible sequelae especially bone fractures [16]. The follow-up protocol included MRI and chest-computed tomography every 6 months for 5 years and then yearly for 10 years. Patients were evaluated by chart review using the Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scales (LENT SOMA) for late toxicity. The study met the guidelines of French law.

Statistical analysis

Follow-up was estimated using the reverse Kaplan–Meier method. The Mann–Whitney *U* test was used to compare numerical values. Overall survival (OS), disease-free survival (DFS), Local relapse (LR), and distant relapse (DR) rates were estimated using the Kaplan–Meier method. The survival rates were defined as the time between the date of pathological diagnosis and the first event. The considered events were death from any cause for OS, death or tumour progression for DFS, and death from the treated cancer or after a relapse for cause-specific survival (CSS). For the LR and DR rates, deaths without relapse were censored, and subsequent relapses after the one considered were not included in the analysis. The 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 were dichotomized. The statistical analyses were performed using SPSS software, version 19 (SPSS Inc., United States). All reported p values are two sided, and p values lower than 0.05 were considered significant.

Results

In total, 414 ESTS patients were managed at our institution for initial treatment ($n = 217$) or re-excision after inadequate initial surgery ($n = 197$). The pathological diagnoses were obtained with a biopsy in 224 (54%) cases or after excision in 190 (46%) cases. The baseline patients' and tumours' characteristics are shown in Table 1. The median tumour size was 8.9 cm (range: 0.8–43). The most frequent location was on the lower limbs (76%), and the most frequent subtype was liposarcoma (29%).

The main treatment patterns are presented in Table 2. Surgery was performed in all of the patients, and 197 (48%) underwent re-excision following prior, unplanned surgery outside our institution. Three patients (1%) underwent amputation. Seventy-six patients required a flap reconstruction (16%). Conservative management required ILP in 62 patients (15%). The median tumour size of patients undergoing their first operation was 10 cm with or without neo-adjuvant treatment (range: 0–43 cm), and 52 patients (13%) had a multifocal tumour. No fragmented resections were performed. In the group of patients who required re-excision after an unplanned initial surgery, 122/197 (62%) presented residual tumour cells. Among all patients, the final quality of the surgery was R0 in 358 patients (82%) and R1 in 76 patients (18%); no resection was R2. The median size of the minimal surgical margin in the R0/residual tumour population (data accessible in 243 patients who had primary surgery or re-excision in our institution) was 2 mm (range: 0.1–30 mm) and 225/243 patients had a minimum surgical margin $\geq$1 mm. In total, 102/414 (25%) had a surgical margin <1 mm.

Out of the whole population of 414 patients, 53 received RT preoperatively (13%, including 7 who also received a postoperative boost) and 361 postoperatively (87%). The median delay between surgery and postoperative RT was 1.9 months (range, 0.5–5.5 mon ths). The median total dose was 50 Gy (range: 36–70 Gy), the median fraction size was 2 Gy/fraction (range: 1.8–3 Gy/fraction), and the median number of fractions was 25 (range: 13–33 fractions). Fifty-five (13%) patients received less than 50 Gy, and 113 (27%) patients had $\geq$60 Gy. A supplementary RT boost was delivered to the high-risk volume in 138 patients at a median dose of 10 Gy (range, 5–20 Gy). R1 patients received a higher dose as compared with R0 patients (median: 60 Gy vs. 50 Gy; $p < 0.001$; Fig. S1). All patients received conformal 3D-RT, except 15 and 5 patients that received 2D-RT and brachytherapy, respectively (at the time of this study, no intensity modulated RT [IMRT] was delivered).

Forty-six per cent ($n = 189$) of the patients received chemotherapy: 88% preoperatively, 12% postoperatively generally before adjuvant radiotherapy and 5% both pre- and postoperatively.

In the entire group, the median follow-up was 6.8 years (range: 0.2–17.6 years). At the final follow-up, 272 patients (66%) were disease-free, 43 patients (10%) were alive with disease, 86 patients (21%) had died of disease progression, and 13 patients had died of an unrelated cause. The 5-year actuarial OS and CSS rates were 80%

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