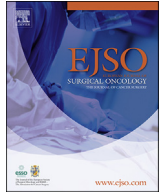




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Identification of predictors for wound complications following preoperative or postoperative radiotherapy in extremity soft tissue sarcoma

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ABSTRACT

Introduction: In extremity soft tissue sarcoma (ESTS), external beam radiotherapy (EBRT) has been used in addition to limb-sparing surgery (LSS). This study aims to identify predictors for major wound complication (MWC) development following EBRT and LSS in ESTS.

Methods: This retrospective study includes ESTS patients treated with EBRT and LSS between 2005 and 2017. Two groups were formed; Group I included preoperatively irradiated patients, whereas Group II included patients who underwent postoperative EBRT. Multivariate logistic regression analyses were performed to create a prediction model for MWC development.

Results: One hundred twenty-seven patients were included, 58 patients (45.7%) in Group I and 69 patients (54.3%) in Group II. Some differences in baseline characteristics were found between the groups, e.g. in tumor size and grade, histological subtype and total RT dose. Twenty-three patients (39.7%) in Group I and 14 patients (20.3%) in Group II developed a MWC ($p = 0.02$). Preoperative EBRT was identified as independent predictor for MWC development, OR 2.75 (95%CI 1.21–6.26), $p = 0.02$. Furthermore, a trend towards an increased MWC risk was shown for patients' age (OR 1.02 (0.99–1.04)), delayed wound closure (OR 3.20 (0.64–16.02)) and negative surgical margins (OR 2.26 (0.72–7.11)). The area under the curve (AUC) of the model was 0.68 (0.57–0.79).

Conclusions: This study corroborates the increased MWC risk following preoperative EBRT in ESTS. It remains important to carefully weigh the MWC risk against the expected long-term functional outcome, and to consider the liberal use of primary plastic surgical reconstructions in an individualized multidisciplinary tumor board prior to treatment.

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Introduction

Annually, approximately 600–700 patients are diagnosed with a soft tissue sarcoma (STS) in The Netherlands [1]. STS are heterogeneous tumors including multiple histopathologic subtypes. Approximately 50–60% of the STS arise in the extremities [2,3].

In the past, extremity soft tissue sarcoma (ESTS) treatment traditionally involved limb-amputation. However, comparable disease-free and overall survival rates were shown for patients treated either with amputation or wide local excision and postoperative radiotherapy [4,5]. Therefore, limb-sparing treatment for ESTS has been the treatment of choice.

External beam radiotherapy (EBRT) has been used in addition to limb-sparing surgery (LSS) to gain local control in ESTS patients; a local control rate of 90% can be achieved nowadays [5–9]. However, despite extensive studying no significant differences in local control and survival between patients treated either with preoperative

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or postoperative EBRT and LSS have been shown to date [10–15]. So, the timing of the EBRT has been subject of debate. Nonetheless, the limb-sparing treatment of ESTS has undergone a gradual transition from postoperative to preoperative EBRT at our institution, mainly based on the data provided by the randomized trial by O'Sullivan et al. [11]. The predominant disadvantages of postoperative EBRT may be the larger radiation fields, higher radiation doses and the increased risk for long-term fibrosis [14]. Accordingly, the use of preoperative EBRT has been advocated for two reasons; smaller radiation fields and lower total radiation doses, possibly leading to an improved functional outcome [16]. The predominant disadvantage of preoperative EBRT is the increased risk for postoperative wound complications [10,11,14,17,18].

The current study aims to identify predictors for the development of postoperative wound complications in ESTS patients following pre- or postoperative EBRT and LSS.

Methods

Patients

The Institutional Review Board approved this retrospective study (case number 2016.676). This study includes ESTS patients over 18 years of age who underwent either pre- or postoperative EBRT and LSS at the University Medical Center Groningen (UMCG) between January 2005 and December 2016. All patients were treated with curative intent. Patients with 'locally advanced' ESTS treated with a combination of hyperthermic isolated limb perfusion, surgical resection and radiotherapy were excluded [19,20]. Furthermore patients with a medical history of Li-Fraumeni syndrome or neurofibromatosis were excluded. Relevant data were obtained from patient medical records. Patients' age at start of treatment is presented, and the maximum tumor diameter prior to start of treatment was used as tumor size. Tumor location was determined as follows: lower leg including the knee, upper leg including the hip, lower arm including the elbow and upper arm including the shoulder.

Prior to treatment, all STS patients are presented in a multidisciplinary sarcoma tumor board to discuss the appropriate treatment strategy for each patient. Two groups were identified; Group I included patients treated with preoperative EBRT and LSS, whereas Group II included patients treated with postoperative EBRT and LSS. All STS patients treated at the UMCG are referred to and treated by a physiotherapist and a rehabilitation specialist to optimize functional outcome following their treatment.

Radiotherapy

All patients underwent EBRT, either in the pre- or postoperative setting. Three-dimensional conformal radiotherapy (3D-CRT) was delivered with a 6–15 MV linear accelerator after patient-specific immobilization, bolus material was applied along the surgical scar. One patient was treated with intensity modulated radiotherapy (IMRT). For Group I, the diagnostic MRI scan was fused with the radiotherapy planning CT scan to obtain gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV). For Group II, the preoperative MRI scan, planning CT scan, surgical scar and markers (left at the surgical bed during the surgical resection) were used to obtain the clinical target volume (CTV) and planning target volume (PTV).

Delineation of the tumors was performed as described in the review by Haas et al. [14]. Although these recommendations were published in 2012, they were already in use before that time. For Group I this meant that the CTV was constructed by expanding the GTV by 4 cm in the longitudinal direction and 1.5 cm in the other

directions. Next, the PTV was obtained by expanding the CTV by 1.0 cm in all directions. The total radiation dose in Group I was 50 Gy (25×2 Gy). In case of a positive surgical margin following preoperative EBRT, no postoperative boost was considered, as this does not seem to influence local control rates [21].

For Group II, the CTV was acquired by expanding the surgical volume by 4 cm in the longitudinal direction and 1.5 cm in all other directions. Next, the PTV was obtained by expanding the CTV by 1.0 cm in all directions. The postoperative EBRT was completed with a 5×2 Gy boost to the tumor bed, resulting in a total postoperative radiation dose of 60 Gy. A boost of 10×2 Gy was applied in case of a R1/R2 resection.

Limb-sparing surgery (LSS)

For Group I, LSS was scheduled to take place six weeks after completion of the EBRT, whereas for Group II the EBRT was planned to start 6–8 weeks after the LSS, provided sufficient wound healing. Plastic surgical reconstructions were performed when indicated, e.g. for primary wound closure or following a wound complication requiring secondary wound closure. The Union for International Cancer Control "R classification" was used to classify the 'quality' of the resection [22].

All complications, either medical or surgical, occurring within 120 days of LSS were analyzed and scored according to Clavien-Dindo [23]. Furthermore, the occurrence of major wound complications (MWC) was monitored. A MWC was defined as a wound complication requiring any of the following, based on the study by O'Sullivan et al. [11]. First, requiring a surgical intervention for wound repair e.g. debridement, abscess drainage and secondary wound closure through plastic surgical flap reconstruction or split skin graft (SSG). Second, requiring non-surgical wound management including: invasive procedure with or without regional anesthesia (e.g. seroma aspiration), readmission for the intravenous administration of antibiotics. Third, requiring persistent deep wound packing (>120 days) or requiring hyperbaric oxygen therapy to obtain wound closure. As hyperbaric oxygen treatment is intensive and generally takes 30–40 daily sessions, these wound complications were included as MWC. Furthermore, these wound complications were scored as a grade IIIa complication [23].

Typing and grading of all histopathologic specimens, either diagnostic core needle biopsies or specimens following LSS, were performed and defined according to WHO and American Joint Committee on Cancer criteria [24,25].

Statistical analyses

Discrete variables are presented with frequencies and percentages and continuous variables with medians and interquartile ranges. Mann-Whitney *U* test was used to compare continuous and ordinal variables. Fisher's exact or chi-square test were used when appropriate to compare nominal variables, *p*-values <0.05 indicating statistical significance. Multivariate logistic regression analyses was performed to create a prediction model for MWC development. Potential predictors were included in a first multivariate logistic regression model. Backward selection was used, and predictors with a *p* < 0.2 were included in the model, 1000x bootstrapping was performed. Odds ratios (OR) and 95% confidence intervals (95% CI) are presented for the model. Subsequently, the area under the curve (AUC) was calculated to determine the predictive value of the final model. SPSS Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp) and Stata/SE version 12.0 (StataCorp, Texas, USA) were used for statistical analyses.

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