European Journal of Surgical Oncology 44 (2018) 816–822

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

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

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ARTICLE INFO

Article history:
Accepted 2 February 2018
Available online 9 February 2018

Keywords:
Soft tissue sarcoma
Extremity
Radiotherapy
Wound complications
Predictors

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.

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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https://doi.org/10.1016/j.ejso.2018.02.002
0748-7983/

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 $\times$ 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 $\times$ 2 Gy boost to the tumor bed, resulting in a total postoperative radiation dose of 60 Gy. A boost of 10 $\times$ 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.

Results

A total of 127 patients, 74 male (58.3%) and 53 female (41.7%) with a median age of 62.0 (48.0–73.0) years, were included. Group I included 58 patients (45.7%) and Group II included 69 patients (54.3%). Patients in Group I had larger tumors which were more often of low grade. An unequal distribution of histological subtypes was observed among the groups. Accidental marginal resections performed at referring institutions account for the difference in local tumor presentation. No differences at baseline were found for age, gender, body mass index (BMI), smoking, diabetes mellitus and distant presentation (Table 1). Two patients in Group II were diagnosed with regional disease at presentation. Both were diagnosed with a lymph node metastasis, and were treated with curative intent by a lymph node dissection in addition to the LSS and postoperative EBRT.

The distribution of patients according to the year of treatment differed significantly among the two groups ($p < 0.001$). Between 2005 and 2007, one patient underwent preoperative EBRT while 35 patients underwent postoperative EBRT in this time period. Whereas, 35 patients underwent preoperative EBRT and four patients underwent postoperative EBRT between 2014 and 2016. In Group I, the median time between completion of EBRT and LSS was 7.0 (6.0–9.3) weeks. In Group II the median time between LSS and start of EBRT was 6.0 (5.0–7.0) weeks. Total EBRT dose differed between Group I and II ($p < 0.001$), and the operation time was longer for patients in Group I, 91.0 (58.0–129.5) vs. 70.0 (48.0–103.0) minutes, $p = 0.027$. No differences considering EBRT technique (3D-CRT vs. IMRT), resection quality, timing or type of wound closure and the use of reconstructive surgery, either primary or secondary, were found. Among the series, a total of seven patients (5.5%) underwent delayed wound closure awaiting the final pathology report. Primary wound closure was achieved in 47 patients (81.0%) and 58 patients (84.1%) in Group I and II respectively. A split skin graft was used for wound closure in five patients (8.6%) in Group I and in eight patients (11.6%) in Group II. Vascularized tissue was used for wound closure in the remaining six patients (10.3%) in Group I and three patients (4.3%) in Group II. However, in Group I an extra two patients ultimately required reconstructive surgery to obtain wound closure due to the development of a MWC (13.8% in total in Group I) (Table 2).

Table 1
Patient, tumor and disease characteristics.

Characteristic	Group I (n = 58)	Group II (n = 69)	p-value
Age (years)	58.0 (45.8–68.3)	65.0 (52.0–74.0)	0.066
Gender			0.774
Female	25 (43.1)	28 (40.6)	
Male	33 (56.9)	41 (59.4)	
BMI	26.9 (23.6–30.0)	25.6 (23.9–27.8)	0.349
Smoking[a]			0.502
No	49 (84.5)	62 (89.9)	
Yes	8 (13.8)	7 (10.1)	
Diabetes mellitus			0.582
No	53 (91.4)	61 (88.4)	
Yes	5 (8.6)	8 (11.6)	
Tumor size (cm)	8.0 (5.8–11.0)	5.0 (3.0–8.0)	<0.001
Tumor grade[b]			<0.001
Low	22 (37.9)	8 (11.6)	
High	35 (60.3)	60 (87.1)	
Tumor location			0.086
Lower leg	15 (25.9)	15 (21.7)	
Upper leg	35 (60.3)	31 (44.9)	
Lower arm	3 (5.2)	9 (13.0)	
Upper arm	5 (8.6)	14 (20.3)	
Histological subtype			<0.001
Myxoid liposarcoma	22 (37.9)	4 (5.8)	
Leiomyosarcoma	5 (8.6)	8 (11.6)	
Myxofibrosarcoma	17 (29.3)	23 (33.3)	
Pleomorphic/NOS	8 (13.8)	15 (21.7)	
Synovial sarcoma	0 (0)	7 (10.1)	
MPNST	1 (1.7)	3 (4.3)	
Other	5 (8.6)	9 (13.0)	
Local presentation			<0.001
First	55 (94.8)	47 (68.1)	
Recurrent	2 (3.4)	4 (5.8)	
R2 resection elsewhere	1 (1.7)	18 (26.1)	
Distant presentation			0.500
M0	58 (100.0)	67 (97.1)	
M1	0 (0)	2 (2.9)	

Data presented as: n (%); median (interquartile range). Group I: preoperative EBRT; Group II: postoperative EBRT.
[a] Data for one patient in Group I missing.
[b] Data missing for one patient in both groups.

Complications

A total of 53 complications in Group I and 42 complications in Group II occurred. Thirty-four patients (58.6%) in Group I and 35 (50.7%) in Group II developed at least one complication ($p = 0.475$). Fifteen patients (25.9%) in Group I and six patients (8.7%) in Group II developed >1 complication. Grade II was the predominant complication grade for both groups. Twenty-three patients (39.7%) in Group I and 14 patients (20.3%) in Group II developed a MWC ($p = 0.02$) (Table 3).

The following variables: age, gender, local presentation, histologic subtype, tumor location, tumor size, tumor grade, BMI, smoking, diabetes, operation time, type wound closure, timing wound closure (delayed vs. direct), reconstructive surgery (only including patients for whom vascularized tissue was used for initial wound closure), radiotherapy timing (preoperative vs. postoperative), and tumor margin (R0 vs. R1/R2) were included in the initial model. Multivariate analyses identified preoperative EBRT as predictor for MWC development, OR 2.75 (1.21–6.26), $p = 0.02$. A trend towards an increased MWC risk was found for age OR 1.02 (0.99–1.04), $p = 0.18$, timing of wound closure (delayed vs. direct) OR 3.20 (0.64–16.02), $p = 0.16$ and tumor margins (R0 vs. R1/R2) OR 2.26 (0.72–7.11), $p = 0.16$ (Table 4). The predictive value of this model i.e. the AUC is 0.68 (0.57–0.79) (Fig. 1).

Discussion

This study shows a significantly increased MWC risk following preoperative EBRT and LSS in ESTS, as nearly 40% of the patients in Group I and 20.3% of the patients in Group II developed a MWC ($p = 0.02$). Multivariate logistic analyses identified preoperative EBRT as significant predictor for MWC development. This finding corroborates earlier reported data [11,14,17,26]. Furthermore, a trend towards an increased MWC risk was shown for elderly patients, patients who underwent an R0 resection and patients who underwent delayed wound closure.

ESTS patients' survival is not influenced by the timing of the EBRT [11–15]. Therefore, the rationale for the timing of EBRT has been based on patient specific variables. These variables comprise expected short- and long-term treatment-induced morbidity e.g. tumor size, tumor depth, radiation dose, timing of the EBRT and also tumor histology i.e. the proven radiosensitivity of myxoid liposarcomas. During preoperative EBRT the tumor volume of some STS increases, however, this increase in volume does not seem to influence local control rates [27]. Several studies, including the randomized trial by O'Sullivan et al., showed significantly more acute wound complications following preoperative EBRT when compared to postoperative EBRT. These studies show that approximately 30–35% of the preoperatively irradiated patients develop a postoperative MWC, compared to approximately 10–20%

Table 2
Treatment-related characteristics.

Characteristic	Group I (n = 58)	Group II (n = 69)	p-value
Year of treatment			<0.001
2005–2007	1 (1.7)	35 (50.7)	
2008–2010	10 (17.2)	21 (30.4)	
2011–2013	12 (20.7)	9 (13.0)	
2014–2016	35 (60.3)	4 (5.8)	
Operation time (min)	91.0 (58.0–129.5)	70.0 (48.0–103.0)	0.027
Size resection specimen (cm, diameter)	13.0 (9.0–16.0)	11.5 (7.0–15.8)	0.135
Total EBRT dose[a] (Gy)	50.0 (50.0–50.0)	60.0 (60.0–70.0)	<0.001
EBRT technique			0.457
3D-CRT	57 (98.3)	69 (100)	
IMRT	1 (1.7)	0 (0)	
Resection quality, tumor margin			0.406
R0	48 (82.8)	54 (78.3)	
R1	10 (17.2)	13 (18.8)	
R2	0	2 (2.9)	
Timing wound closure			0.701
Direct	54 (93.1)	66 (95.7)	
Delayed awaiting pathology report	4 (6.9)	3 (4.3)	
Type wound closure			0.386
Primary	47 (81.0)	58 (84.1)	
Split skin graft	5 (8.6)	8 (11.6)	
Vascularized tissue	6 (10.3)	3 (4.3)	
Reconstructive surgery (primary or secondary)			0.059
No	50 (86.2)	66 (95.7)	
Yes	8 (13.8)	3 (4.3)	
Timing reconstructive surgery			
Direct	4	3	
Secondary awaiting final pathology report	2	0	
Secondary due to MWC	2	0	
Type reconstructive surgery			
Free flap	1	0	
Pedicled flap	7	3	

Data presented as: n (%); median (interquartile range). Group I: preoperative EBRT; Group II: postoperative EBRT.
Abbreviations: EBRT = external beam radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity modulated radiotherapy.
[a] All patients in Group I underwent 50 Gy (25 × 2 Gy) EBRT. In Group II: 67 patients (97.1%) underwent 60–70 Gy EBRT. One patient in Group II underwent an hyperfractionated EBRT schedule of 30 × 1.8 Gy resulting in a total dose of 54 Gy. The second patient developed a local recurrence and distant metastases during the postoperative radiation therapy and the EBRT was aborted after a local palliative dose of 50 Gy.

of patients following postoperative EBRT [10,11,14,17,18,26]. On the contrary, due to the often larger radiation field-size and higher radiation dose, postoperative EBRT is associated with higher risk of fibrosis, joint stiffness and edema during long-term follow-up. The presence of these late complications leads to an impairment in patients' functional outcome [16].

At our institution a tendency towards the use of preoperative EBRT has taken place during the last years. Hence, in the current study only one of the 36 patients treated between 2005 and 2007 underwent preoperative EBRT, whereas 35 of the 39 patients treated between 2014 and 2016 underwent preoperative EBRT. Preoperative EBRT seems supported by a recent cost-effectiveness analysis, due to more costly postoperative EBRT-induced long-term morbidity [28]. However, there are also data showing that patients' functional outcome is adversely affected by the development of a postoperative MWC [29,30]. Therefore, the cost-effectiveness of preoperative radiotherapy might be questioned.

In myxoid liposarcoma, preoperative EBRT has become standard due to its proven radiosensitivity [31,32]. Accordingly, a radiotherapy dose reduction study in myxoid liposarcoma (NCT02106312) was initiated and first results are awaited. This dose reduction of preoperative EBRT (total dose of 36 Gy) might subsequently result in a decreased MWC risk in this specific histological subtype. Besides dose reduction, preoperative hypofractionated EBRT (5 × 5 Gy) followed by LSS within one week also seems to be effective in myxoid liposarcoma [33].

Hypofractionated EBRT has been studied and used more commonly in other cancers, e.g. breast and rectal cancer [34,35]. Data on hypofractionated EBRT in extremity and trunk STS is scarce. A study by Kosela et al. showed that oncological outcome was comparable following 5 × 5 Gy hypofractionated preoperative EBRT and LSS within one week, when compared with the commonly used 25 × 2 Gy regimen [36]. Only 7% of the patients in this study required a surgical intervention for the treatment of a wound complication. Furthermore, preoperative hypofractionated EBRT in STS is under ongoing investigation in a phase II trial (NCT02701153), of which the preliminary results were recently presented at the Connective Tissue Oncology Society Annual Meeting, 2017, showing a MWC rate of 17% in these patients [37].

The current study has some limitations. The small sample size and the retrospective nature of the study harbors the risk of selection bias and missing data. Unfortunately, we were unable to identify and include the patients who were scheduled for LSS and postoperative EBRT, but who failed to undergo the scheduled EBRT. However, we were able to retrieve the patients who were scheduled for preoperative EBRT and LSS who did not undergo LSS. These 8 patients underwent preoperative EBRT, but failed to undergo LSS due to various reasons i.e. local tumor progression during the preoperative EBRT resulting in a non-resectable tumor in one patient, development of distant metastases during EBRT resulting in a palliative setting in five patients and declining health status during EBRT resulting in a situation in which LSS was not feasible in two patients. Although all patients were referred to and treated by a physiotherapist and a rehabilitation specialist, no standardized long-term functional outcome was obtained. Therefore, we were unable to include patients' functional outcome in this study. Moreover, there were some differences in baseline- and treatment characteristics between both groups. Patients in Group I had larger

Table 3
Complications for Group I and II according to Clavien-Dindo [23].

	Group I (n = 58)	Group II (n = 69)	p-value
Total amount of complications	**53**	**42**	
Grade I	**10 (18.9)**	**11 (26.2)**	
Medical	*2*	*2*	
Collapse	1	0	
Urinary retention	1	2	
Surgical	*8*	*9*	
Seroma	4	6	
Neuropraxia	2	1	
Delayed wound healing	1	2	
Hematoma	1	0	
Grade II	**18 (34.0)**	**14 (33.3)**	
Medical	*4*	*5*	
Atrial fibrillation	2	0	
Anemia	1	2	
Pulmonary embolism	1	1	
Deep venous thrombosis	0	1	
Urinary tract infection	0	1	
Surgical	*14*	*9*	
Infection needing oral antibiotics	11	7	
Infection needing intravenous antibiotics	3	0	
Delayed wound healing	0	1	
Split skin graft loss[a]		1	
Grade IIIa	**9 (17.0)**	**12 (28.6)**	
Infection	2	4	
Seroma	2	5	
Wound dehiscence	0	1	
Hematoma	0	2	
Delayed wound healing (hyperbaric O2)	5	0	
Grade IIIb	**12 (22.6)**	**5 (11.9)**	
Infection	9	1	
Total flap loss	1	0	
Partial flap necrosis	1	0	
Postoperative bleeding	1	3	
Compartment syndrome	0	1	
Grade IV	**2 (3.8)**	**0 (0)**	
Systemic sepsis	1	0	
Postoperative arterial bleeding	1	0	
Grade V	**2 (3.8)**	**0 (0)**	
Systemic sepsis	1	0	
Esophageal ischemia	1	0	
Total patients developing a complication	34 (58.6)	35 (50.7)	0.475
Patients developing a MWC	23 (39.7)	14 (20.3)	0.020

Data presented as: n (%); Group I: Preoperative EBRT; Group II: Postoperative EBRT.
[a] The split skin graft used for wound closure was lost and removed during an outpatient clinic visit, resulting in delayed wound healing. The complications accounting for the MWCs are indicated in gray for both groups.

tumors, which might explain the longer operation time, but more importantly this might also partly explain the higher amount of MWCs in Group I. However, neither tumor size nor operation time were identified as independent predictor for MWC development in

Table 4
Final prediction model for the development of a major wound complication.

Predictor	OR	95% CI	p-value
Radiotherapy timing			0.02
Postoperative	1		
Preoperative	2.75	1.21–6.26	
Age, continuous	1.02	0.99–1.04	0.18
Timing wound closure			0.16
Direct	1		
Delayed	3.20	0.64–16.02	
Tumor margins			0.16
R1/R2	1		
R0	2.26	0.72–7.11	

Data presented as OR and 95% CI, age in years.
Abbreviations: OR = odds ratio; CI = confidence interval.

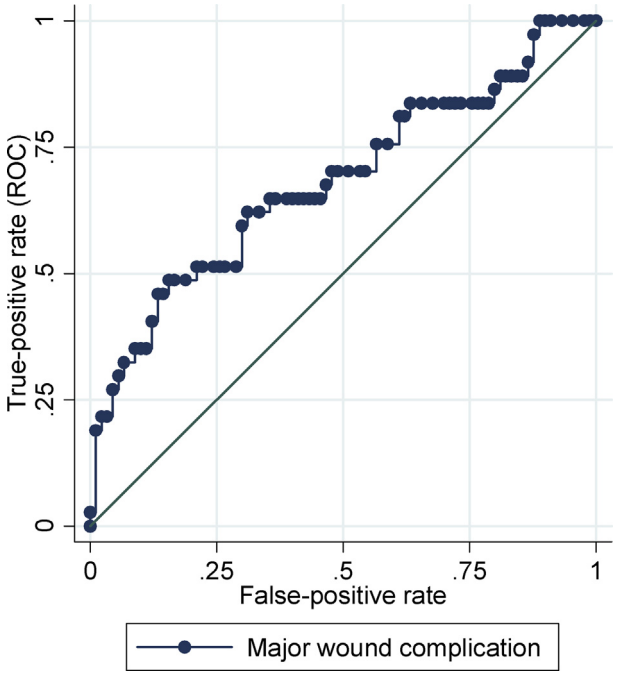

Fig. 1. Receiver operating characteristic (ROC) curve for the development of a major wound complication. Area under the curve is 0.68 (0.57–0.79).

the current study. Histological subtype differed between the groups, with significantly more low grade tumors in Group I. Since 20 of the myxoid liposarcomas (90.9%) included in Group I were low grade sarcomas, the larger proportion of myxoid liposarcomas in Group I might account for the difference in histological subtype as well as for the difference in tumor grade between the groups. The prediction model for MWC development should be interpreted with caution, the relative small sample size and low amount of events, 37 MWCs in total, influence the predictive value and the AUC for the ROC-curve of the model. However, the model identified preoperative EBRT as significant predictor for MWC development, although some residual confounding might be present. The fact that elderly patients, or patients who underwent delayed wound closure tend to have a higher MWC risk seems reasonable. We cannot explain the association between R0-resections and the increased MWC risk. Possibly, bias plays a role, where preoperatively irradiated patients have an increased MWC risk but also a higher chance to undergo a R0-resection [38], but we could not show a difference in margin status in our series.

STS management and outcome can be improved by further centralization of sarcoma treatment [3,39]. The multidisciplinary evaluation of patient- and tumor characteristics, as well as expected short- and long-term treatment-induced morbidity prior to the start of treatment results in an individualized approach [40]. Furthermore this dedicated sarcoma treatment might facilitate a more liberal and consequent use of primary reconstructive surgery which might lower the MWC risk in preoperative irradiated patients [26,41,42]. Hence, in patients who underwent flap reconstruction, preoperative EBRT was not associated with MWC development [43]. Moreover, early involvement of the plastic surgeon might enable the radiation oncologist to spare skin and soft tissue, i.e. consider them as 'organ at risk', which are planned to be used for the plastic surgical reconstruction.

Further studies considering the 'protective' influence of primary reconstructive surgery as well as studies comparing hypofractionated EBRT with conventionally fractionated EBRT are necessary [44].

Conclusions

This study corroborates the increased MWC risk following preoperative radiotherapy and LSS when compared with postoperative radiotherapy and LSS in ESTS. Therefore, 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 ESTS treatment.

Conflict of interest statement

The authors have no disclosures of commercial interest to declare.

Acknowledgements

M.G. Stevenson received a research grant from the Groningen Melanoma Sarcoma Foundation.

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