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Review

Risk factors for postoperative wound complications after extremity soft tissue sarcoma resection: A systematic review and meta-analyses

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Abstract *Introduction:* Advancements in imaging, surgical, and radiation techniques have made resection of larger and more extensive extremity soft tissue sarcomas (ESTS) possible but with the potential for high complication rates. This study summarizes complication and reoperation rates associated with resection of ESTS and reviews predictors for wound complications.
Methods: A systematic review of the literature on ESTS in adults was undertaken from the four databases MEDLINE, Embase, MEDLINE In-Process & Other Non-Indexed Citations, and the Cochrane Central Register of Controlled Trials (CCRCT). Meta-analyses of the complications, reoperations, and risk factors were performed.
Results: In the twenty-one studies included, there was an overall wound complication rate of 30.2% (95% CI 26.56–33.47) and a reoperation rate of 13.37% (95% CI 10.21–16.52) in 5628 patients. Individual studies reported that older patient age, obesity, smoking, diabetes, large tumor size, tumor site, and preoperative radiotherapy were associated with adverse outcomes.

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Tumors of the lower limb, diabetes, smoking, obesity, and radiation were identified as independent predictors of wound complications in meta-analysis. A high level of heterogeneity between studies limited pooled analysis for many variables.
Conclusions: Despite advancements in the treatment of ESTS, postoperative complication rates remain high. Awareness of the risk factors for wound complications, especially those that may be modifiable, is essential to decrease postoperative morbidities in these patients to improve treatment outcomes and quality of life.

Contents

Introduction

Soft tissue sarcomas are rare neoplasms that most commonly affect the extremities[1-3]. In the past, it was believed that amputation of the affected limb was necessary to prevent local recurrence and improve survival rates.[4,5] However, studies since the 1980s have indicated that wide surgical resection combined with radiotherapy could achieve comparable oncological results while facilitating limb preservation.[6-10] Over the past 30 years, improvements in imaging, surgical, and radiation techniques together with an increased focus on multidisciplinary care have made limb preservation possible in approximately 90% of patients.[11-16] As more extensive tumors are now considered resectable, the complexity of soft tissue sarcoma surgery has increased, and consequently, it might be expected that more patients would experience postoperative complications.[17,18]

Like many rare conditions, the risks and consequences of sarcoma surgery are poorly characterized.[19-23] Increasing complexity of surgery coupled with wider adoption of preoperative radiation means that these patients are at particularly high risk for postoperative wound healing complications that can delay recovery and rehabilitation and compromise functional outcomes.[14,24-26] As extensive resections have become the standard of care, it is essential that surgeons recognize the complications that may occur and the associated contributing factors so that patients may

be appropriately counseled preoperatively. There is an increasing demand for accurate and personalized risk assessment in surgical care, and this will require comprehensive and disease-specific knowledge of complications and their causes.

The objectives of this systematic review and meta-analyses were (1) to provide an overview of the published work focusing on wound complications following extremity soft tissue sarcoma (ESTS) surgery, (2) to investigate the (independent) risk factors for postoperative wound complications in the same patient group and (3) to investigate whether meta-analysis of the results was possible to establish pooled estimates of the wound complication rates, reoperation rates, and the independent risk factors for wound complications.

Methods

Search strategy

The Cochrane and PRISMA guidelines for the conduct of systematic reviews were followed for this study. In preparation for the search, a preliminary review of the literature was performed to determine the characteristics and quantity of published literature describing postoperative wound complications in soft tissue sarcoma (STS) surgery. A research librarian developed and executed a comprehensive computer-aided search strategy, including the following databases to search for publications of the medical literature: MEDLINE, Embase, MEDLINE In-Process & Other Non-Indexed Citations, and the Cochrane Central Register of Controlled Trials (CCRCT). The following key words and their synonyms were combined in the search strategy: [Sarcomas, Soft Tissue Neoplasms, Connective Tissue Neoplasms] and [Extremities] and [Surgical Procedures, Operative, Surgical Specialties, Surgical Flaps, Postoperative Complications, Intraoperative Complications]. Concepts commonly related to postoperative complications, including Postoperative Care, Postoperative Period, and Anesthesia Recovery Period were also used. For a detailed search strategy, see Supplemental Table 1. Retrieval was restricted to articles written or translated in English, but no time limitations were applied. We excluded case study reports, animal studies, health-care professionals' views or experiences, reviews of literature, medical procedures or specific technology advancements, guidelines, meeting presentations, and consensus or conference reports.

The search was performed on August 8, 2016.

Eligibility and study selection

Two researchers (JS and AH) independently screened the article titles, abstracts, and full-texts. Any publications thought to be potentially relevant by either reviewer were retrieved and reviewed in full text. In the full-text screening stage, studies were included when both reviewers felt they met all the inclusion criteria. Disagreements were resolved through discussion and consensus with a third author (AON). The following criteria were applied: (1) a sample of at least ten patients with soft tissue sarcomas of the extremity (ESTS) were analyzed, (2) the individuals studied underwent a surgical procedure, (3) postoperative complications were defined as a main outcome, and (4) multivariate analyses of risk factors for complications were performed. There was no restriction in study design. Studies that included STS of other anatomical locations were included if the majority of cases in the study involved the extremities. Reports including bone sarcomas or studies that solely included tumors that were initially inoperable but were excised after treatment with neoadjuvant radiation, chemotherapy, or hyperthermic isolated limb perfusion were excluded, as these cases have an extensively higher risk of developing complications.

Data extraction and analysis

Each paper was read carefully, and data were extracted on the study author, publication year, study location, study population, location of the tumor, study design, objectives, and inclusion and exclusion criteria. The primary outcomes of this study were the proportion of postoperative wound complications and reoperations. Secondary outcomes were the recorded risk factors for wound complications. In some cases, the authors of the original articles were contacted to obtain unreported data. All risk factors for wound complications that were significant in multivariate analyses of at least 1 paper were included in the systematic review (Table 2).

Four studies did have minor overlap in their patient populations.[27-30] However, as this overlap was not substantial, all of these studies were included in the meta-analyses on postoperative wound complications and reoperations. In addition, as there was no overlap in the analysis of independent risk factors, all selected studies were included in meta-analyses of the risk factors for complications.

Wound complication and reoperation rates with associated odds ratios (OR) and corresponding 95% confidence intervals (CIs) for all risk factors were extracted and entered in a datasheet. Meta-analyses were performed for wound complications, reoperations, and the associated risk factors with the METAPROP and METAN command using STATA/SE version 12.0 (StataCorp, College Station, Texas, USA). The overall wound complication rates and reoperation rates of all included studies were then pooled using a random effects model. Publications were stratified at study level by the anatomical location of the tumor so that subgroup analyses of the separate STS locations could be performed. In addition, meta-analyses of all risk factors for wound complications that were found to be significant in uni- or multivariate analyses of at least two papers were performed. No pooling of risk factors for reoperations was performed due to insufficient data. Pooling of results was performed using either a random-effects or a fixed-effects model, depending on the number of included studies and the degree of heterogeneity (I^2) observed. An I^2 $<25\%$ was considered as low heterogeneity, between 25% and 50% moderate, and $>50\%$ high heterogeneity. To determine statistical heterogeneity that was quantified by the I^2 statistic, the chi-square test was used. Two-sided *P*-values <0.05 were considered to be significant.

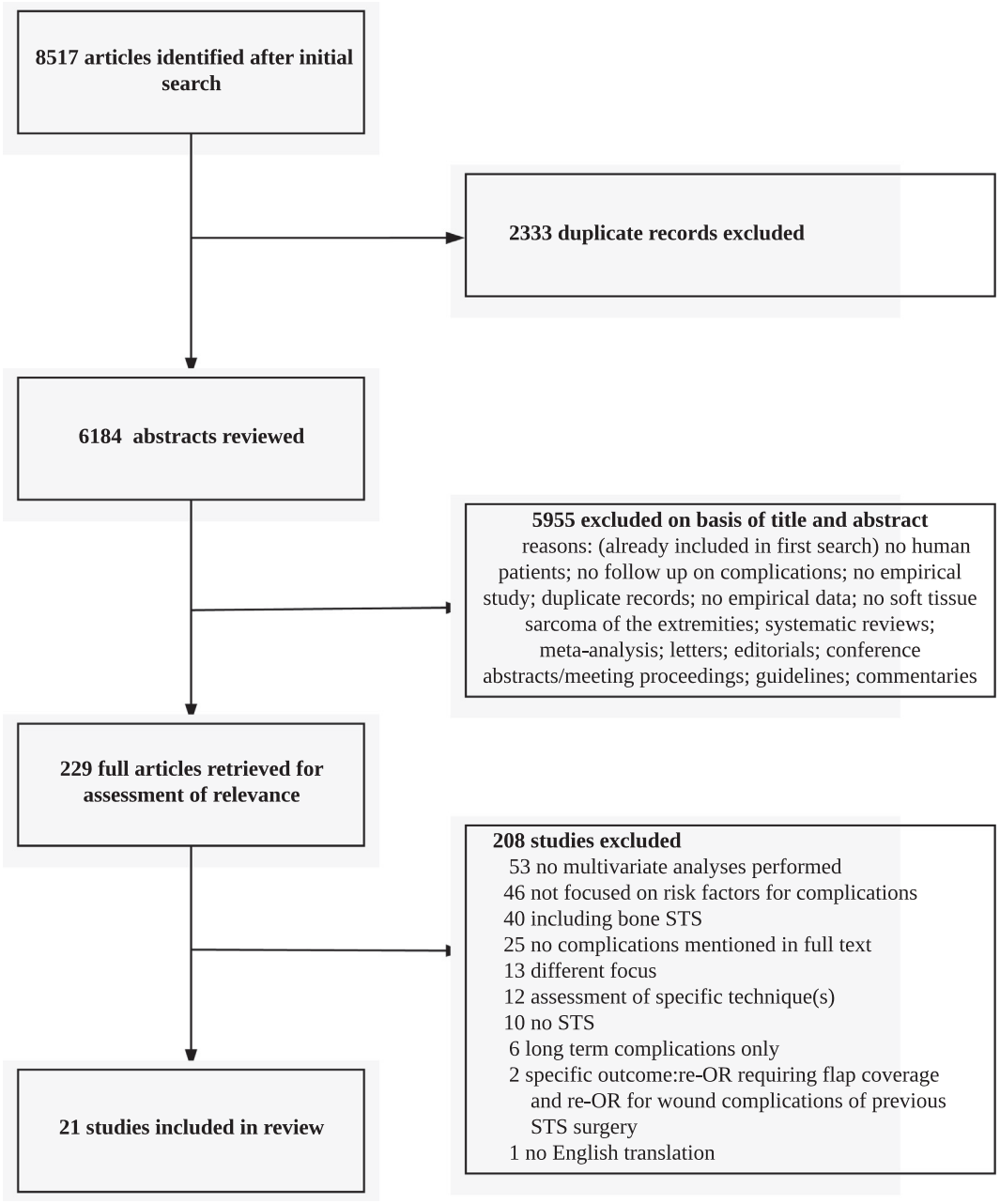

Figure 1 Diagram of study selection.
Flowchart summarizing the search strategies and subsequent selection of studies for the systematic review.

Results

Literature search

A flowchart of the study selection is shown in Figure 1. The literature search identified a total of 8517 articles, of which 2333 were found to be duplicates and were excluded, which resulted in a total of 6184 unique articles for review. Two reviewers independently applied exclusion and inclusion criteria and selected 229 papers for full-text review. Finally, a total of twenty-one studies were included in this systematic review.

Study characteristics

Table 1 shows the characteristics of the twenty-one studies included in this review. The articles were published between 1993 and 2019, reporting on a total of 5628 patients. All but one publication[11] used a retrospective study design, and the majority included extremity cases only (12 of 21 papers), but the inclusion criteria varied between studies (Supplementary Table 2). Where reported, 97% of patients presented with a primary tumor (ranging from 86% to 100% in 18 studies), whereas 3% required excision of a local or regional recurrence (ranging from 0 to 14% in

Table 1 Overview of characteristics of included studies.

Year	Authors	Study design	Center	n	Research goal	STS Site	P/LR	Tumor size mean^ median#	PC%	RS%	RT% (%pre/%post)	Chemo%	Outcomes	WC rate (%)	*Re*-OR (%)
STS location in extremity															
2002	O'Sullivan[11]	RCT	M	182	PC/RS + pre vs. postop RT	E	P(91%) LR (9%)	-	71.4	28.6	100 (48/52)	0	WC + LC + OS	25.8	10.4
2005	Alektiar[29]	RR	S	369	PC in high-grade STS + postop RT (RT/BRT)	E	P (100%)	-	100	0	100 (postop)	34	WC requiring re_OR + long-term WC + LC + OS + DMFS	-	7.9
2006	Cannon[14]	RR	S	412	PC/RS + pre vs. postop RT	Lower E	P (100%)	# 8 cm (1.2-30)	79.6	20.4	100 (65/35)	41	WC (acute and chronic)	27.4	8.5
2009	Rimner[28]	RR	S	255	PC + postop RT (RT/BRT)	Thigh	P (100%)	-	100	0	100 (postop)	31	WC requiring re-OR + long-term WC + LC + OS + DMFS	-	9.4
2010	Davidge[26]	RR	M	247	PC vs. RS +/- RT (pre/postop)	E	P (94%) LR (6%)	^ 7.7 cm (1.7-13.6)	77	23	75 (69/13)	0	WC + FS	25.1	10.1
2012	Korah[13]	RR	S	118	PC + pre vs. postop RT	E	P (100%)	# 7.6 cm (0.8-30)	100	0	100 (81/19)	29	WC + LC + OS + DMFS	33.1	21.2
2013	Rosenberg[31]	RR	S	73	PC/RS + preop RT	E	P (100%)	^ 12.2 cm (-)	61.6	38.4	100 (100/8)	18	WC + LC + OS	31.5	16.4
2016	Ziegele[27]	RR	S	81	PC/RS +/- RT (pre/postop)	Thigh +pelvis	P (100%)	-	62	38	90 (86/4)	69	WC	32	-
2016	Miller[33]	RR	S	102	PC/RS + RT (pre/postop)	E	P (93%) LR (7%)	# 8 (1.5-23) cm	78	22	100 (25/75)	39	WC	21.5	14.7
2017	Slump[34]	RR	S	897	PC vs. RS + RT (pre/postop)	E	P (93%) LR (9%)	-	70.3	29.7	? (54/6.1)	5.4	WC	32.9	10.7
2018	Stevenson[22]	RR	S	127	PC/RS + pre vs. postop RT	E	P (95.3%) LR (4.7%)	# 6.4 cm	91.3	8.7	100 (45.7/54.3)	?	WC	48	16.5
2018	Lansu[35]	RR	S	191	PC/RS + preop RT	E	P (95.8) LR (4.2)	^ 10.55 cm	68.6	31.4	100 (preop)	1.05	WC + LC + OS	31.4	16.2
STS location in extremity + trunk +/- head and neck															
1993	Bujko[40]	RR	S	202	PC/RS + preop RT +/- postop RT	*E + T + H*	P (86%) LR (14%)	-	89	11	100(100/71)	24	WC	36.6	16.5

(*continued on next page*)

Table 1 (*continued*)

Year	Authors	Study design	Center	n	Research goal	STS Site	P/LR	Tumor size mean^ median#	PC%	RS%	RT% (%pre/%post)	Chemo%	Outcomes	WC rate (%)	*Re*-OR (%)
1994	Peat[25]	RR	S	180	PC vs. RS +/- RT (pre/postop)	*E* + *T*	-	# 90cm[2]	76	24	- (31/ -)	18	WC requiring re-OR + LC	-	16
2013	Baldini[39]	RR	M	103	PC/RS + preop RT	*E* + *T*	P (91%) LR (9%)	# 8.4 cm (2-25)	70	30	100 (preop)	18	WC	35	25.2
2014	Moore[32]	RR	S	256	PC/RS +/- RT (pre/postop)	*E* + *T* + *H*	-	# 9 cm (0.5-40)	72	28	67 (48/24)	15	WC	17.6	-
2015	Bedi[30]	RR	S	92	PC/RS + preop RT	*E* + *T*	P(100%)	-	56	44	100 (preop)	38	WC	25	23.9
2016	Saeed[36]	RR	S	196	PC/RS + preop RT (3D-CRT vs. IMRT)	*E* + *T*	P (100%)	# 9.08 cm	?	?	100 (preop)	36.2	WC	28.6	-
2017	Broecker[37]	RR	S	546	PC/RS +/-RT	*E* + *T*	P (100%)	^ 9.6 (± 6.9) cm	49.6	50.4	? (35/10)	23	WC + LR + OS	29.1	13
2017	Stoeckle[38]	RR	S	728	PC/RS +/- RT	*E* + *T*	P (100%)	^ 9.8 (± 6.8) # 8 (0.8-60)	87	13	70 (0.4/80)	28	WC + OS + FS	40.9	2.1
2018	Karthik[21]	RR	S	271	PC/RS +/- RT	*E* + *T*	?	# 8.6 (1-47)	86	14	39.9 (15.9/24)	?	WC (acute and chronic) + LR + OS	22.1	-

RR: retrospective review, RCT: randomized controlled trial, S: single center, M: multicenter, PC: primary closure, RS: reconstructive surgery, RT: radiotherapy, BRT: brachyradiotherapy, 3D-CRT: 3-D conformal radiotherapy, E: Extremities (both upper and lower), T:trunk, H:Head and neck, P: primary tumor, LR: Local recurrence, LC: local control, OS: overall survival, DMFS: distant metastasis-free survival, FS: functional status, WC: wound complication, re-OR: reoperation; preop: preoperative; postop: postoperative.

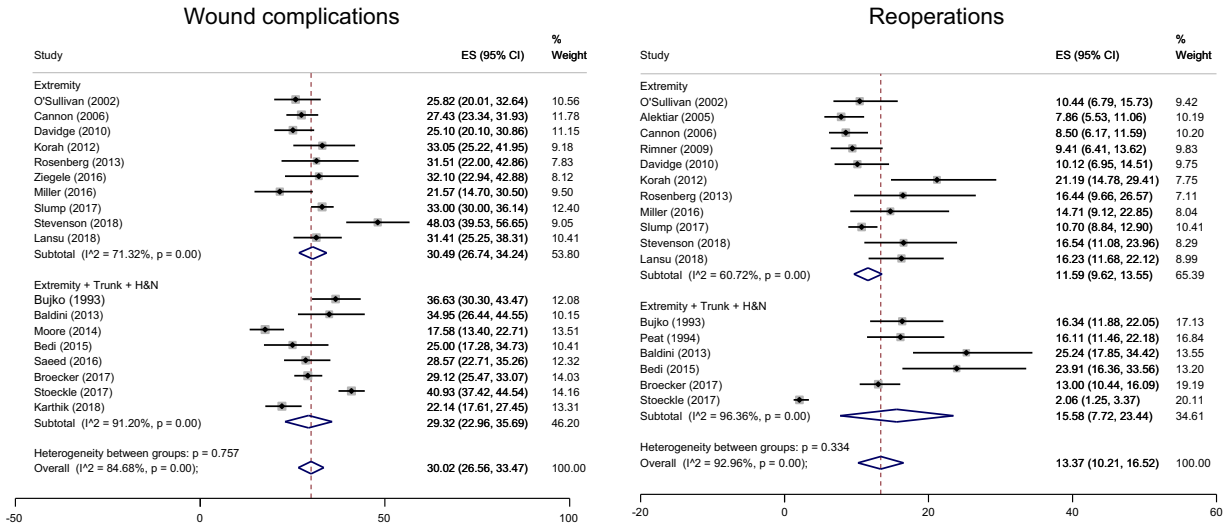

Figure 2 Pooled wound complication and reoperation rates.
ES: Effect size; CI: confidence interval; H&N: head and neck; I^2: Degree of heterogeneity (I^2 <25% = low; I^2 25%–50% = moderate; I^2 >50% = high). P-values <0.05 were considered to be significant.

18 studies).[11,13,32-39,14,22,26-31] The treatment modalities varied among the studies; however, all treatment regimens included pre- or postoperative radiation therapy. Six studies only included preoperatively irradiated patients,[30-32,36,37,40] while two other studies only included postoperatively radiated patients.[28,29] Excluding these eight studies, the proportion of either pre- or postoperatively radiated STS patients ranged from 39% to 90% of the study population in the other 13 studies.[11,13,35,38,39,14,21,22,25-27,33,34] The mean percentage of patients treated with preoperative radiation was 40% (range: 0.4–86%) and postoperative radiotherapy was administered in 29% of the patients (range: 4–70%) in these studies. The proportion of patients treated with chemotherapy was low (20%, ranging from 0 to 69%, 19 studies). Overall, 77% (range: 49.6–100%, 20 studies) of patients underwent primary wound closure while soft tissue reconstructive surgery was required in 23% (range: 0.5–0.4%, 20 studies) of the cases.

The included studies reported the overall wound complication rate, reoperation rate, and risk factors for either wound complications or reoperations. These outcomes are also utilized in this systematic review.

Wound complications

In 2002, O'Sullivan et al. introduced a definition of major wound complications,[11] which has been adopted by nine of the included studies.[13,14,22,27,30-32,34,37] Three other studies used different criteria, some of which were partly based on the definition of O'Sullivan and colleagues.[26,33,40] Three studies solely reported wound complications requiring a reoperation.[25,28,29] All definitions of complications are shown in Supplementary Table 2. Wound complication rates were reported in eighteen studies and varied from 17.6% to 48%. Meta-analyses identified an overall wound complication rate of 30.2% (95% CI 26.56–33.47, 18 studies [11,13,33-40,14,21,22,26,27,30-32]) with high heterogeneity (I^2 84.68%, Figure 2). Sub-analyses of the studies stratified for tumor location showed an overall wound complication rate of 30.49% (95% CI 26.74–34.24, I^2 71.32%, 10 studies [11,13,14,22,26,27,32,34-36]) in the extremity only studies and 29.32% (95% CI 22.96–35.69, I^2 91.20%, 8 studies [21,30,31,33,37-40]) in those including STS located in the extremity, as well as the trunk and head and neck.

Reoperations

The reoperation rate was reported in seventeen studies and ranged from 2.1% to 25.24%. Meta-analyses of these rates are displayed in Figure 2 and show an overall reoperation rate of 13.37% (95% CI 10.21–16.52, 17 studies [11,13,32,34-36,38-40,14,22,25,26,28-31]). However, owing to high statistical heterogeneity (I^2 92.96%), stratification on tumor location was performed. This resulted in lower heterogeneity with a reoperation rate of 11.59% (95% CI 9.62–13.55, I^2 60.72%, 11 studies [11,13,36,14,22,26,28,29,32,34,35]) in the extremity-only group and a slightly higher reoperation rate of 15.58% (95% CI 7.72–23.44, I^2 96.36%, 6 studies[25,30,31,38-40]) in the studies including extremity, trunk, and head and neck STS.

Risk factors for wound complications

All recorded risk factors for wound complications and their associated odds ratios (OR) are presented in Table 2. To show the independent effect of each risk factor and its effect in relation to other variables, both univariate and multivariate results are shown. The study of Baldini et al. included STS located in the extremity and trunk and also performed sub-analyses on the extremity-only cases, and these results are shown separately in Table 2.[31]

All risk factors for wound complications with at least two observations (OR and 95% CI) in uni- or multivariate analysis were subsequently included in the meta-analyses. Where

Table 2 Overview of all included risk factors and odds ratios (OR) for complications and reoperations.

Study	n	Outcome	Patient/tumor factor	Odds Ratio (OR)		Treatment factor	Odds Ratio (OR)	
				UVA	MVA		UVA	MVA
STS location in extremity								
O'Sullivan[11] 2002	182	WC	Age (continous)	NR	ns	Reconstructive surgery	0.94	ns
			Gender	NR	ns	Preoperative vs. postop RT	2.60*	3.08*
			Presentation (first/recurrence)	NR	ns			
			Tumor size > 10 cm	s	1.11*			
			Prior incomplete resection	NR	ns			
			Lower extremity location	16.7*	10.4*			
Alektiar[29] 2005	369	*Re*-OR	Lower extremity location	12.48*	NR*			
Cannon[14] 2006	412	WC	Age (continous)	NR	ns	Reconstructive surgery	1.51	
			Tumor size >5 cm	2.21*	s*	Vascular reconstruction	NR	ns
						Bone exposure	NR	ns
						Periostal stripping	NR	ns
						Preoperative vs. postop RT	2.67*	s*
Rimner[28] 2009	255	*Re*-OR	Age >50	2.76*	s*	Vessel resection	2.97*	s*
			Gender	ns	ns	Postoperative chemotherapy	ns	
			Tumor size >10 cm	ns	ns	RT type (EBRT vs BRT)	s*	s*
			Thigh compartment location^	3.19*	ns			
Davidge[26] 2010	247	WC[1] & *Re*-OR[2]	Age (continous)	NR	1.02[1]*	Reconstructive surgery	1.52[1]/1.72[2]	0.78[1]
			Prior incomplete resection	NR	0.84[1]	Bone resection	NR	4.06[1]*
			Tumor size (continous)	NR	1.08[1]*	Preoperative RT	NR	2.67[1]*
			Tumor stage 3	NR	1.28[1]			
Korah[13] 2012	118	WC[1] & *Re*-OR[2]	Tumor size >8cm	NR	s[1]*	Preoperative vs. postop RT	s[1,2]*	s[1]*
			Lower extremity location	1.29[1]*/2.85[2]*	s[1,2]*			
Rosenberg[31] 2013	73	WC[1] & *Re*-OR[2]	Age (continous)	ns[1,2]		Reconstructive surgery	1.41[1]/0.67[2]	
			Female gender	1.89[1]/4.29[2]*	ns[1]/0.96[2]*	Involvement plastic surgeon	0.67[1]/0.35[2]	
			Smoking	1.85[1]/2.55[2]		Preoperative chemotherapy	0.68[1]/0.37[2]	
			Weight	ns[1,2]		RT dose/fractation (180 vs 200 Gy)	1.88[1]/1.39[2]	
			Diabetes	2.69[1]/1.52[2]		RT outside institution	1.89[1]/3.69[2]*	ns[1]/1.11[2]*
			Tumor size (continous)	1.074[1]*/1.02[2]	NR			
			High tumor grade	0.28[1]/0.24[2]*	ns[1]/0.85[2]*			
			Lower extremity location	3.17[1]/6.66[2]*	ns[2]			
Baldini[31] 2013	84	WC Extremity group	Age ≥50	ns		Reconstructive surgery	s	ns
			Smoking	s	10.06*			
			Tumor size >10 cm	s	3.3*			
			Tumor proximity (<3 mm to skin)	s	6.8*			
			Lower extremity location	2.19				
	103	Total population	Age ≥50	ns		Reconstructive surgery	2.77*	6.4*
			Smoking	3.21				
			Obesity	ns				
			Diabetes	4.5*	5.6*			
			Tumor size >10 cm	2.94*	6.2*			
			Tumor proximity (<3 mm to skin)	3.9*	3.9*			
Ziegele[27] 2016	81	WC	Age (continous)	ns	ns	Reconstructive surgery	2.34	3.69*
			Smoking	ns	ns	Preoperative chemotherapy	1.18	ns
			BMI > 28.8	1.53	ns	Preoperative RT	ns	ns
			Diabetes	ns	ns			
			Cardiovascular disease	ns	ns			
			Tumor size ≥10 cm	2.11				
			Tumor volume ≥228.1 mL	1.001*	1.001*			
			High tumor grade	ns				
			Tumor proximity (<3 mm to skin)	ns	ns			
Miller[33] 2016	102	WC	Age	ns		Reconstructive surgery	3*	0.95
			Female gender	1.54		Skin graft placement	5.76*	6.39*
			BMI > 30	1.55		Preoperative chemotherapy	0.28	0.26
			Diabetes	5.14*	1.82	Preoperative RT	3.88*	4.29*
			Smoking	0.7		Preoperative RT dose (2.0 vs 1.8 Gy)	5.22*	2.89
			Preoperative albumin < 3.5 g/dl	ns (evt getal)		RT delivery: 2D/3D CRT vs IMRT	ns	
			Presentation (first/recurrence)	1.7				
			Tumour size ≥ 8 cm	1.11				
			High tumour grade	1.15				
Slump[34] 2017	897	WC	Age > 70 years	1.67*	1.3	Reconstructive surgery	1.37*	1.12
			Female gender	0.92		Preoperative RT (yes vs no)	2.61*	2.66*
			Comorbidities	1.51*	1.23	Postoperative RT (yes vs no)	1.27	
			BMI > 30	1.61*	1.79*	Preoperatieve chemotherapy	1.02	
			Lower extremity location	2.48*	2.10*			
			Tumour depth (deep vs superficial)	1.49*	1.13			

(*continued on next page*)

Table 2 (*continued*)

Study	n	Outcome	Patient/tumor factor	Odds Ratio (OR)		Treatment factor	Odds Ratio (OR)	
				UVA	MVA		UVA	MVA
			Tumour size ≥ 10 cm	1.67*	1.02			
			Tumour volume ≥ 650 cm^3	2.25*	1.37			
			High tumour stage (≥ 3)	2.43*	1.16			
Stevenson[22]	127	WC	Age (continous)	NR	1.02	Preoperative vs postoperative RT	NR	2.75*
2018						Delayed wound closure	NR	3.20
						Tumour margins (R1/R2 vs R0)	NR	2.26
Lansu[35]	191	WC	Age (continous)	0.99				
2018			BMI ≥ 30	3.59*	4.05*			
			Hypertension	1.15				
			Diabetes	1.60				
			Smoking	3.96*	4.59*			
			Lower extremity location	2.36	4.98*			
			Tumour size > 10 cm	0.68				
			Tumour depth (deep vs superficial)	0.35*	0.24			
STS location in extremity + trunk +/- head & neck								
Bujko[40]	202	WC[1] &	Age ≥60	1.94[1]*/1.73[2]		Postoperative chemotherapy	0.73[1]/0.41[2]	
1993		*Re*-OR[2]	Age (continous)	s[1,2]*	1.00[1]*	Postoperative RT boost	ns[1,2]	
			Female gender	0.61[1]/0.47[2]		Preoperative RT dose	ns[1,2]	
			Obesity	0.87[1]/1.03[2]		2 fractions preop RT/day	1.94[1]*/1.52[2]	1.84[1]*
			Diabetes or cardiovacular disease	1.39[1]/1.04[2]		Time interval preop RT	ns[1,2]	
			Presentation (first/recurrence)	1.34[1]/1.26[2]		Blood loss ≥1000 ml	3.12[1]*/2.04[2]	2.94[1]*
			Tumor size ≥10cm	1.28[1]/1.08[2]	ns[1]			
			High tumor grade	3.38[1]*/1.95[2]	ns[1]			
			Lower extremity location	3.57[1]*/9.39[2]*	3.77[1]*			
Peat[25]	180	*Re*-OR	Age (continous)	ns		Reconstructive surgery	0.31	
1994			Smoking	3.38*	ns	Preoperative RT	3.34*	s
			Diabetes or cardiovascular disease	4.68*	ns			
			Tumor volume >100 cm^2	6.94*	s			
			Lower extremity location	1.19				
Moore[32]	256	WC	Age (continous)	ns		Reconstructive surgery	1.07	
2014			Female gender	1.13		Bone resection	ns	
			Smoking	2.71*	3.49*	Any chemotherapy	0.87	ns
			BMI ≥ 30	2.50*	2.76*	Preoperative RT	2.3*	2.46*
			Diabetes	4.71*	4.07*	RT dose	ns	
			Cardiovascular disease	s	ns	Time interval preop RT	ns	
			Hypercholesterolemia	s	ns			
			Tumor size >10 cm	3.16				
			Tumor size (continous)	1.06*	1.05*			
			Tumor depth	2.62	ns			
			High tumor grade	3.02				
			Proximal lower extremity	2.94*	3.00*			
Bedi[30]	92	WC	Age (continous)	ns		Reconstructive surgery	ns	
2015			Gender	ns		Flap type	ns	
			Smoking	ns		Involvement plastic surgeon	ns	
			BMI (continous)	ns		Preoperative chemotherapy	ns	
			Diabetes	ns		Vascular resection	s	ns
			Cardiovascular disease	ns		Time interval preop RT	ns	
			Tumor size (continous)	ns		Biopsy outside institution	3.33*	5.79*
			Tumor depth	ns				
			High tumor grade	ns				
			Lower extremity location	s	16.66*			
Saeed[36]	196	WC	Age	ns		Reconstructive surgery	ns	
2016			Gender	ns		Chemotherapy	ns	
			Diabetes	ns		IMRT vs 3-D CRT	s	0.4*
			Cardiovascular disease	ns				
			Smoking	ns				
			Tumour size	ns				
			Lower extremity location	s	7.14			
Broecker[37]	546	WC	Age (continous)	1.03*	1.03*	Reconstructive surgery	1.69	
2017			Female gender	1.08		Preoperative RT	1.51*	0.87
			BMI (continous)	1.02		Postoperative RT	0.52	
			ASA class 4	1.21		Postoperative chemotherapy	1.37	
			Comorbidities	1.64*	1.21	Intraoperative drain placement	1.56*	0.94
			Tumour size (continous)	1.07*	1.07*	Operation time	1.007*	1.004*
			Lower extremity location	1.28		Neurovascular or bone resection	1.47	

(*continued on next page*)

Table 2 (*continued*)

Study	n	Outcome	Patient/tumor factor	Odds Ratio (OR)		Treatment factor	Odds Ratio (OR)	
				UVA	MVA		UVA	MVA
			Tumour depth (deep vs superficial)	1.46		Resection status (R2 vs R0/R1)	2.99*	
			High tumor grade	2.05*	1.91			
			Tumour depth (deep vs superficial)	1.46				
Stoeckle[38]	728	WC	Age	ns		Neurovascular or bone resection	2.08*	ns
2017			Gender	ns		Preoperative radiotherapy	ns	
			ASA class 3	2.88*	4.0*	Postoperative radiotherapy	ns	
			Tumour size 8 cm	3.28*	2.5*	Preoperative chemotherapy	2.37*	ns
			Multifocal/multicompartimental	2.17*	2.0*	Postoperative chemotherapy	ns	
			Lower extremity/trunk location	4.25*	4.1*			
			Tumour depth (deep vs superficial)	3.27*	ns			
			Tumour grade	ns				
			Type of biopsy	ns				
Karthik[21]	271	WC	Age (continous)	1.0		Reconstructive surgery	1.97	2.04
2018			Female gender	1.29		Preoperative radiotherapy	1.86*	1.92*
			Smoking	0.93		RT dose	1.00	
			Extemity location(vs trunk)	4.76*	2.95*			
			High tumor grade	0.99				
			Tumour size (continous)	1.03	1.03			

UVA: univariate analysis; MVA: multivariate analysis; WC: wound complication; *Re*-OR: re-operation; s: significant (no information about OR); ns: not significant (no information about OR);.
NR: not reported; RT: Radiotherapy; 3D-CRT: 3-D conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; *denotes statistical significance; ^Medial/posterior thigh compartment vs. anterior compartment.
[1]: risk factor for wound complications; [2]: risk factor for requiring a *Re*-OR.

Table 3 Summary of the meta-analyses.

Variable	Model	N	Pooled OR (95% CI)	Heterogeneity (I^2)	*P*-value
Smoking	MVA	2	3.95 (2.15-7.27)	Low	0.66
Diabetes	MVA	3	3.56 (1.70-7.43)	Low	0.54
Lower Limb	MVA	5	3.22 (1.87-5.53)	Moderate	0.18
Preoperative radiation (vs. postoperative radiation)	MVA	2	2.92 (1.67-5.12)	Low	0.84
Obesity	MVA	3	2.37 (1.44-3.89)	Medium	0.23
Preoperative radiation (yes vs. no)	MVA	6	2.06 (1.34-3.17)	High	0.04*
Flap Reconstruction	MVA	6	1.69 (0.95-3.00)	High	0.01*
Tumor size $\geq$ 10 cm	MVA	3	1.55 (0.78-3.110	High	0.009*
Tumor size (continuous)	MVA	4	1.06 (1.03-1.08)	Low	0.44
Age	MVA	3	1.02 (1.01-1.03)	Low	0.71
Comorbidities	UVA	2	1.62 (1.25-2.11)	Low	0.95
Tumor Grade	UVA	6	1.53 (0.82-2.87)	High	0.006*
Tumor Depth	UVA	3	1.15 (0.34-3.90)	High	<0.001*
Chemotherapy	UVA	3	1.07 (0.4202.69)	High	0.006*

UVA: univariate analysis; MVA: multivariate analysis; N/A: not applicable; OR: odds ratio; N/A: not applicable.
I^2: Degree of heterogeneity (I^2 <25% = low; I^2 25%–50% = moderate; I^2 >50% = high).
**P*-values <0.05 were considered to be significant.

possible, the results of multivariate meta-analysis are reported below. In cases where multivariate data were insufficient, the results of univariate meta-analysis are reported. The results of all pooled data analyses are shown in Figure 3, and a summary of these findings are shown in Table 3. Data on risk factors for reoperations were insufficient to perform meta-analyses.

Age

Age was evaluated in all but two publications [13,29] and was included in the multivariate analyses of nine studies. In univariate analysis, age was significant in four studies [28,35,38,40] and not significant in eleven publications; [21,25,41,27,31-34,36,37,39] four publications did not report on their univariate findings.[11,14,22,26] In multivariate analysis, older age was found to be an independent predictor for wound complications or reoperations in four of nine studies.[26,28,38,40] Age was not found to be significantly associated with complications in multivariate analyses of the remaining five studies.[11,14,22,27,35] Pooling of these results showed an univariate OR of 1.01 (95% CI 0.98-1.03, I^2 82.6%, Figure 3) and a multivariate OR of 1.02 (95% CI 1.01-1.03, I^2 0.0%, Figure 3). Pooling of the remaining data

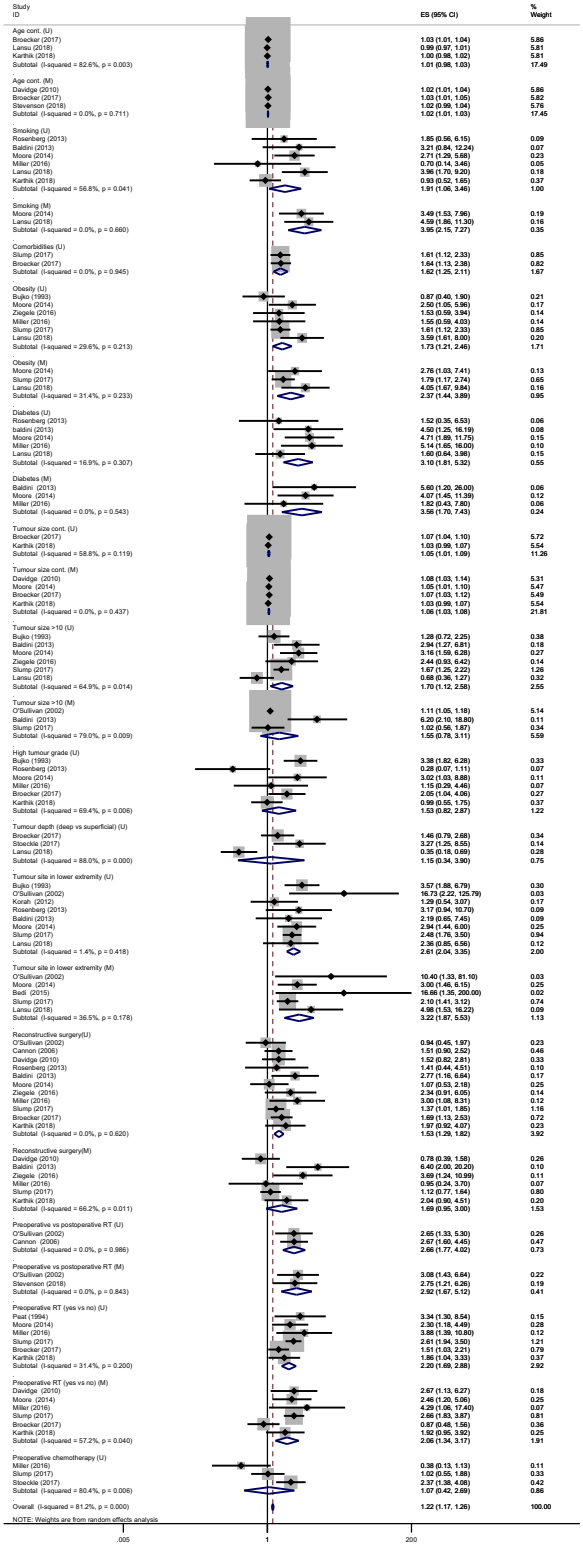

Figure 3 Pooled analyses – Risk factors for complications, stratified by risk factor.
ES: Effect size; CI: confidence interval; U: univariate analysis; M: multivariate analysis; RT: radiotherapy; I^2: Degree of heterogeneity (I^2 <25% = low; I^2 25%–50% = moderate; I^2 >50% = high). P-values <0.05 were considered to be significant.

was not feasible due to either incomplete data or the use of different cut-off points (e.g., 50 years, 60 years, or 70 years).

Smoking

The effect of smoking was evaluated by univariate analysis in six studies[25,27,30-33] and subsequently included in multivariate analysis of four[25,27,31,33];three of these studies showed a significant effect of smoking on wound complications on both univariate and multivariate analyses.[31,33,36] Peat et al. reported a significant effect of smoking on reoperation rates on univariate analysis but not on multivariate testing.[25] Rosenberg et al. found a significant univariate effect but did not include smoking in multivariate analysis,[32] and the five remaining studies found no significant effect of smoking on complications.[21,27,30,34,37] The univariate OR of six studies[21,31-34,36] was pooled with an overall OR of 1.91 (95% CI 1.06–3.46, I^2 56.8%, Figure 3) and the pooled multivariate OR was 3.95 (95% CI 2.12–7.27, I^2 0.0%, 2 studies,[33,36] Figure 3).

Comorbidities

The majority of the reports included specific comorbidities (e.g., obesity, diabetes, and cardiovascular disease); however, two studies grouped these comorbidities together as one variable to identify the impact on wound complications.[35,38] In both of these studies, the presence of one or more comorbidities was significantly related to complications in univariate analysis, however, not on multivariate testing. Pooling of the univariate results showed an OR of 1.62 (95% CI 1.25–2.11, I^2 0.0%, Figure 3).

Obesity

BMI was included in univariate analysis in ten studies [27,30-36,38,40] and multivariate analysis in four of these.[27,33,35,36] In univariate analysis, obesity was not significantly related to wound complications in five studies.[30-32,34,38] Three studies reported a significant effect of obesity in both univariate and multivariate analyses,[33,35,36] while the study of Ziegele et al. showed significance on univariate testing only.[27] In comparison, Bujko and colleagues reported no association between obesity and wound complications but showed a significant effect on reoperation rates in univariate analysis.[40] The majority of the authors defined obesity as BMI >30 kg/m^2; however, Ziegele and colleagues [27] used their median BMI of 28 kg/m^2 as the cutoff point and Broecker et al. used it as a continuous variable. Six studies [27,33-36,40] were suitable for univariate pooling, and demonstrated an overall univariate OR of 1.73(95% CI 1.21–2.46, I^2 29.6%, Figure 3), and three studies[33,35,36] showed a pooled multivariate OR of 2.37(95% CI 1.44–3.89, I^2 31.4%, Figure 3).

Diabetes

The effect of diabetes was evaluated in univariate analyses in ten studies [25,27,30-34,36,37,40] and in multivariate

analyses in five of these studies.[25,27,31,33,34] Diabetes was found to be a significant univariate predictor of wound complications in three studies, which remained significant in multivariate analyses in two publications.[31,33] Six reports did not find any significant effect on univariate testing.[27,30,32,36,37,40] Miller and colleagues reported a significant effect of diabetes on wound complications on univariate analysis but not on multivariate testing.[34] Bujko et al. and Peat et al. grouped diabetes together with cardiovascular diseases, making them unsuitable for pooling with the other studies.[25,40] Two studies were not pooled due to missing information.[27,30] Pooled analyses in Figure 3 show an overall univariate OR of 3.10(95% CI 1.81-5.32, I^2 16.9%, 6 studies[27,33-36,40]) and a multivariate OR of 3.56 (95% CI 1.70-7.43, I^2 0.0%, 3 studies,[31,33,34]).

Tumor size

All but two authors[22,29] evaluated tumor size in univariate analyses and all of these except three[34,36,37] subsequently included this factor in multivariate analyses (Table 2). Even though various cutoff points were used (5, 8, or 10 cm, and size as a continuous variable or as a measure of volume), tumor size was a significant independent predictor for either wound complications or reoperations in multivariate analyses in ten of sixteen studies.[11,13,14,25-27,31,33,38,39] Studies using similar cutoff points were included in meta-analyses (Figure 3). Considering tumor size as a continuous variable, the overall multivariate OR was 1.06 (95% CI 1.03-1.08, I^2 0%, 4 studies [21,26,33,38]). Tumors >10 cm showed a multivariate OR of 1.55 (95% CI 0.78-3.11, 3 studies [11,31,35]) but with a high level of heterogeneity (I^2 79%, Figure 3).

Tumor grade

Tumor grade showed significance in three of nine studies by univariate analyses, [21,27,30,32-34,38-40] which included this factor in multivariate analyses.[32,38,40] Rosenberg et al. indicated low tumor grade as a risk factor for reoperations, which remained significant in multivariate analysis.[32] Conversely, Bujko et al. and Broecker and colleagues showed high tumor grade to be associated with wound complications in univariate analysis, but this was not significant in multivariate testing.[38,40] Six studies [21,32-34,38,40] were included in the pooled analyses with an overall univariate OR of 1.53 (95% CI 0.82-2.87, Fig. 3) and with a high level of heterogeneity (I^2 69.4%).

Tumor location

Tumor location was analyzed in all but five reports,[14,22,26,27,34] as shown in Table 2. The study of Rimner et al. focused on thigh sarcomas and demonstrated significantly more complications in the medial and posterior compartment than in the anterior compartment in univariate analysis but not on multivariate analysis.[28] Moore and colleagues identified proximal lower extremity STS as an independent predictor for complications than the upper extremity or head and neck locations.[33] The fourteen remaining studies analyzed the influence of lower versus upper extremity tumor location on wound complication or reoperation rates. In twelve of these studies, lower extremity tumors were associated with significantly more complications or reoperations than upper extremity tumors in univariate analysis,[11,13,39,40,21,27,29,32,33,35-37] and this remained significant in multivariate analyses of ten reports. The pooled multivariate OR was 3.22 (95% CI 1.78-5.53, I^2 36.5%, 5 studies,[11,33,35,36,41] Fig. 3).

Tumor depth

Tumor depth was measured as proximity to the skin (stratified as ≤3 mm, or >3 mm) in four reports [27,30,31,33] as well as deep or superficial to the fascia in five studies.[30,33,36,38,39] Baldini et al. reported that tumor proximity to the skin surface (<3 mm) increased the wound complication rate,[31] but this finding was not confirmed by others. Two studies showed deep tumors to be associated with wound complications in univariate analysis, but this was not significant in multivariate testing.[36,39] Pooled analyses in Fig. 3 show an overall univariate OR of 1.15 (95% CI 0.34-3.90, 3 studies[36,38,39]) with a high level of heterogeneity (I^2 88%).

Flap reconstruction

The influence of soft tissue reconstructive surgery on wound complications or reoperation rates was considered by fifteen studies (Table 2).[11,14,33-35,37,38,21,22,25-27,30-32] One study found significantly increased complication rates following flap reconstruction in both univariate and multivariate analyses.[31] Two studies showed reconstructive surgery to be associated with wound complications in univariate analysis, but this was not significant in multivariate testing.[34,35] Ziegele and colleagues showed significantly more wound complications in patients undergoing flap reconstructions on multivariate analyses.[27] The eleven remaining reports showed no significant differences in wound complication or reoperation rates following flap reconstructions compared to wounds closed primarily. Pooled analyses found a multivariate OR of 1.69 (95% CI 0.95-3.00, 6 studies,[21,26,27,31,34,35] Fig. 3) but with a high level of heterogeneity (I^2 66.2%).

Other reconstructive surgery

The role of vascular involvement was evaluated in both univariate and multivariate analyses of five studies.[14,28,30,38,39] Three of these investigations showed univariate significance for high wound complication rates, and multivariate significance was demonstrated in one study.[28] No results were pooled owing to missing data. Bone resection was reported as an independent predictor for wound complications in one study.[26]

Chemotherapy

The impact of chemotherapy on postoperative wound complications was evaluated in eleven studies. Chemotherapy

was delivered preoperatively,[27,30,32,34,35,37] postoperatively,[28,38,40] or both.[33,39] Only one study[39] found a significant effect of preoperative chemotherapy on wound complications in univariate analysis. Pooled analyses found a univariate OR of 1.07 (95% CI 0.42–2.69, 3 studies[34,35,39]) but with a high level of heterogeneity (I^2 80.4%, Fig. 3).

Radiotherapy

All studies included radiated STS patients, ranging from 39.9% to 100% of the study populations (Table 1). Six studies included either exclusively preoperative radiation or postoperative radiation (Table 2)[28-31,36,37] and did not evaluate the impact of radiotherapy on wound complications. Of the remaining 15 studies, 12 considered the influence of preoperative radiotherapy on wound complications or reoperations in both univariate and multivariate analyses. However, the reference group for preoperative radiotherapy differed among the studies. The reference was the absence of radiation in six studies[21,25,26,33,35,38] and postoperative radiation in six others.[11,13,14,22,27,34] Preoperative radiotherapy showed a significant uni- and multivariate association with increased wound complications compared to postoperative radiotherapy in five of six reports.[11,13,14,22,34] Pooled analyses showed a multivariate OR of 2.92 (95% CI 1.67–5.12, I^2 0.0%, 2 studies,[11,22] Fig. 3). Preoperative radiotherapy compared to no radiotherapy also showed a significant uni- and multivariate association with increased wound complications in four studies [21,26,33,35] and with reoperations in one study.[25] Multivariate pooling showed an OR of 2.06 (95% CI 1.34–3.17, I^2 57.2%, 6 studies [21,26,33-35,38], Fig. 3).

Discussion

This systematic review and meta-analysis provides an overview of the published literature regarding wound complications following ESTS surgery. Although more than one quarter of ESTS patients develop wound complications, the factors that contribute to this are poorly understood. This study shows that a relatively small number of papers have performed comprehensive analysis of risk factors for postoperative wound complications in this population, and among those studies, there was a lack of uniformity in terms of definitions and reporting of outcomes, as well as a high level of methodological variability.

In spite of these limitations, the current literature suggests a number of risk factors contribute to the development of postoperative wound complications in patients who undergo resection of ESTS. The meta-analysis identified smoking and diabetes to be the strongest predictors of postoperative wound complications with a fourfold increase in risk and a very low level of heterogeneity between studies. Obesity was also found to be important, increasing the risk by 2.5-fold. Identification of accurate patient-related predictors of complications is important for preoperative consultation and counseling.[42-44] Although it may not be possible to modify high BMI in the acute cancer setting, patients might be encouraged to cease smoking and optimize glycemic control to reduce the risk of complications. Even in cases where it is not possible to modify these risk factors, understanding their relationship to postoperative outcomes is essential if patients are to receive personalized risk assessment and accurate information of the risks and benefits of cancer treatment.[45]

Tumor location in the lower extremity was the strongest tumor-related predictor of wound complications, increasing the risk threefold compared to lesions in the upper extremity with a relatively low level of heterogeneity between studies.[11,30,33,35,36] The definition of lower limb varied, however, with some studies including tumors of the buttock or pelvis, which may have impacted the results.[25,27,33,40] Larger tumors were also associated with a higher rate of complications, but there was wide variation in how tumor size was defined, which resulted in a high degree of heterogeneity.

The timing of radiation treatment remains a controversial issue in sarcoma management. This study confirmed neoadjuvant radiation doubled the risk of wound complications compared to patients who did not receive any radiation.[26,33]. Preoperative radiation was also shown to increase the risk almost threefold when compared to postoperative radiation. Proponents of neoadjuvant radiation argue that it permits smaller doses and treatment fields, which limits chronic fibrosis and improves long-term functional outcomes.[46] However, these proposed functional benefits clearly come at a cost, as studies consistently show that performing ablative surgery shortly after radiation treatment significantly increases postoperative complication rates. As this review focused only on wound complications consideration of functional outcomes was beyond the scope of our study. However, we have previously reported that postoperative complications can adversely affect long-term functional outcomes following ESTS resection.[47] Variations in radiation protocols make direct comparison between studies challenging. There was insufficient detail in the included papers to consider the effects of other factors such as radiation dose or fractionation on outcomes. There is a clear need for more focused prospective studies to weigh the risks of preoperative radiation against the possible functional benefits.

Although flap reconstruction is often perceived to increase the complexity of surgery and leads to higher rates of complications, this is not supported by this meta-analysis. Most studies included in this review consider patients who undergo primary wound closure and flap reconstruction collectively and as such are inherently flawed. There are fundamental differences between cases where defects can be closed primarily and those that require soft tissue reconstruction with many confounding factors to be considered, and hence, these patient groups must be evaluated separately rather than simply including reconstruction as a risk variable in collective studies. At our center, we have a low threshold for reconstruction in high-risk cases and have previously demonstrated that judicious use of flaps may mitigate the effects of certain risk factors such as lower limb tumors or preoperative radiation. Although the advantages of importing well-vascularized tissues may be obvious to the plastic surgery community, there is a lack of well-designed studies to provide strong evidence for this. There is a need for more high-quality research to demonstrate the benefits of flap reconstruction in particular clinical scenarios so that evidence-based guidelines can be developed and integrated into multidisciplinary preoperative planning.

With increasing focus on personalized cancer care, there is a growing expectation that patients will be provided with accurate and individualized predictions of outcomes before surgery. The current literature provides insufficient evidence to support the development of accurate preoperative risk calculators in ESTS surgery. We have previously reported that significant risk factors differ in upper and lower limb ESTS and that treatment factors such as the use of flap reconstruction may affect the significance of certain risk factors in individual patients.[35] These findings highlight the need for more detailed study on the role of individual risk factors in particular clinical settings. The current literature focuses the impact of multiple individual variables, but as we have previously demonstrated, synergistic interaction between variables can increase rates of postoperative complications in patients with multiple risk factors, and this should be considered in future studies.[20]

The major limitation of this systematic review and meta-analysis is the relatively small number of studies that were eligible for inclusion. In general, few investigations provided adequate data on predictors of complications in either univariate or multivariate analysis. Where meta-analysis was possible, the results were based on the findings of a small number of studies with relatively few patients in most cases. Individual multivariate models included different variables, which may have also affected the strength of our meta-analysis. Because of outcome bias, significant results are generally published more frequently and the majority of studies excluded from the pooled analyses due to missing information had nonsignificant findings. Therefore, the pooled ORs might be overestimated, and the results should be interpreted with a degree of caution.

The inherent variability in the presentation of patients with ESTS and its treatment makes the pooling of data from different studies difficult, and this is reflected in the high level of heterogeneity in the pooled analyses for many variables in this study. Although the heterogeneity of the disease itself cannot be avoided, some limitations of the current data might be addressed with prospective multicenter studies with standardized recruitment criteria and outcome measures. In 2002, the landmark randomized controlled trial of O'Sullivan et al. established criteria for wound complications following ESTS resection that have been adopted by other investigators but with significant modifications in many studies.[11] Furthermore, elements of these criteria may not be consistent with more recent developments in modern wound care such as the use of negative pressure dressings or interventional radiological drainage of fluid collections. Establishing more up-to-date definitions of major and minor wound complications that could be universally adopted would improve the quality of future studies and enable more effective comparison and pooling of data. There was insufficient detail in the included studies to identify specific predictors of serious as major and minor wound problems were considered collectively in most cases.

While this study included a large number of variables, it is not exhaustive and other significant risk factors may not have been considered in the papers chosen for inclusion. In particular, the impact of specific treatment protocols or surgical techniques was not evaluated in this review. In addition, we only considered complications related to postoperative wound healing and did not investigate the rate of other surgical or medical adverse events. However, our previous work and that of others indicates that wound problems account for the vast majority of complications in this patient population.

Conclusion

This systematic review identified a number of patients (diabetes, smoking, and obesity), tumor (size and lower limb), and treatment (radiation) factors that contribute to postoperative wound complications following resection of ESTS. However, in spite of high rates of wound complications, our understanding of risk factors remains poor. This is due in part to the lack of uniformity in the included studies and the high level of heterogeneity observed in our pooled analyses. This highlights the need for improved data quality in future studies in this field and standardized classification and reporting of complications and their associated risk factors.

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Conflict of interest

There is no conflict of interest for any of the authors of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2019.05.041.

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