The role of reconstructive surgery in the treatment of soft tissue sarcomas

Slump, Jelena

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Jelena Slump

Colofon

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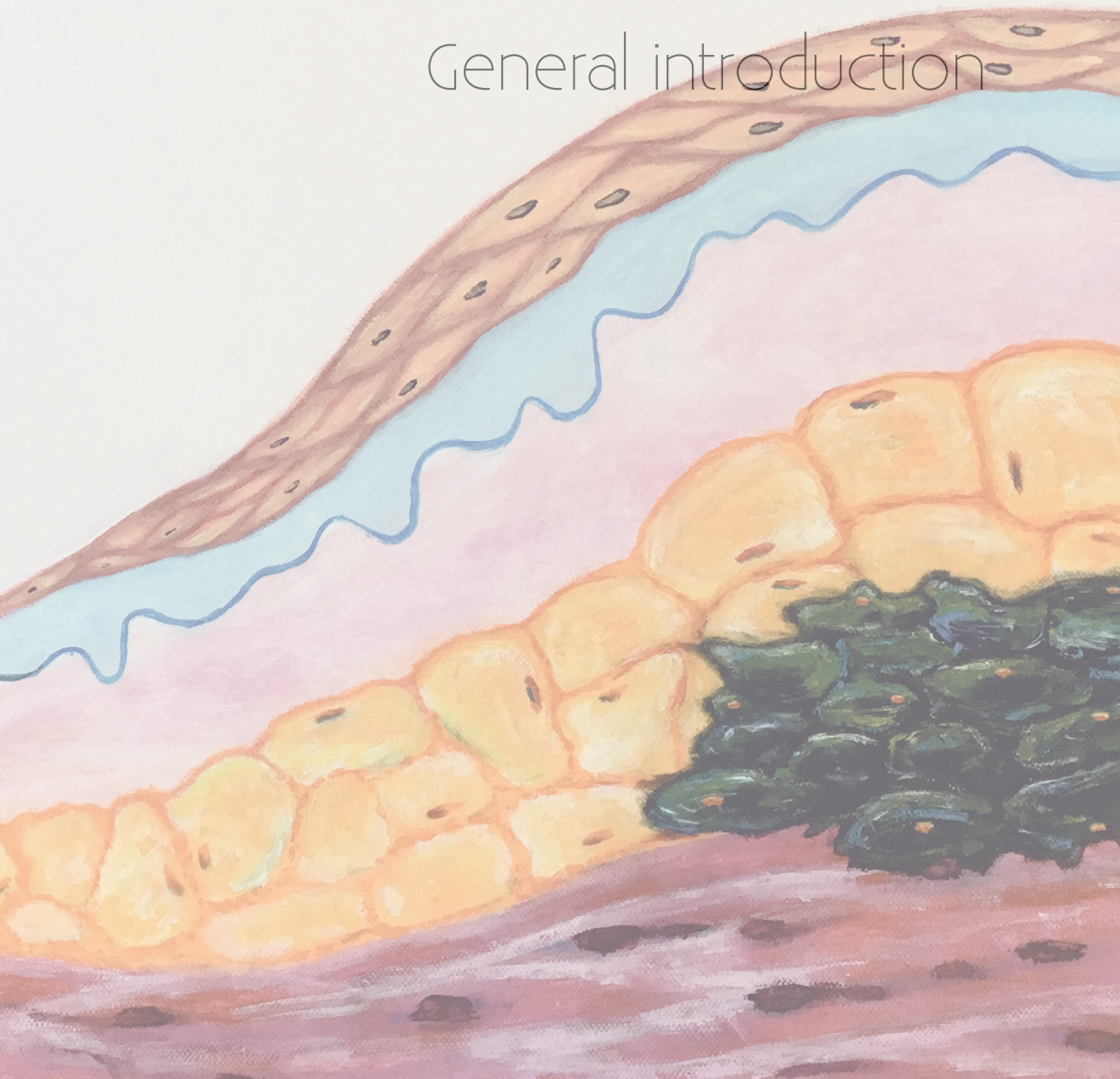
CHAPTER 1

General introduction



Introduction to the thesis

Sarcomas are a rare group of malignant mesenchymal neoplasms, accounting for about 1% of all adult malignancies. Approximately 80 percent of sarcomas originate from soft tissues (including fat, muscle, nerve, and nerve sheath, blood vessels and other connective tissues), and the rest originate from bone.[1–3] This thesis will focus on soft tissue sarcomas (STS). The most common subtypes of STS are shown in Figure 1 and the STS locations are displayed in Figure 2.

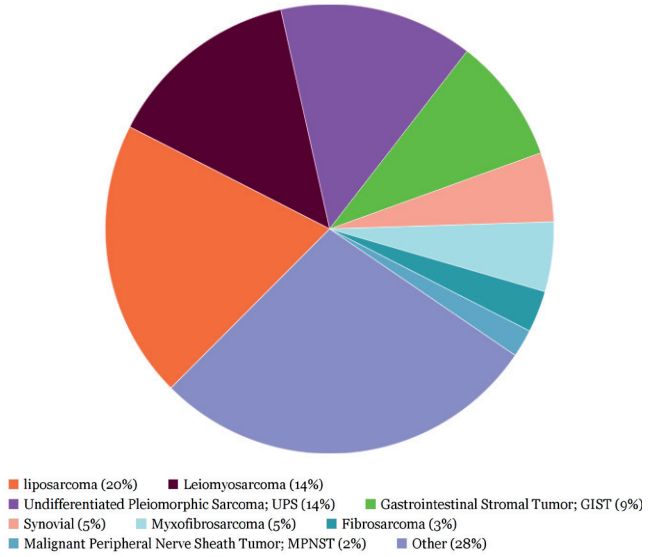


Figure 1. Distribution of STS histologic subtypes
Figure adopted from Brennan et al.[4,5]

The etiology of STS is not fully understood. Most sarcomas are believed to arise spontaneously and not from a pre-existing benign lesion. However, genetics and environmental factors such as radiation therapy or chemotherapy, chemical carcinogens, chronic irritation or inflammation and immunosuppression appear to play a role in the pathogenesis of soft tissues into sarcomas.[6–9]

STS can appear at virtually all anatomic sites of the body, although the most common sites for primary tumours are the lower extremity (28-49%), upper extremity (12-

21%), retroperitoneum (8-15%), head and neck (4-13%), abdomen (10-12%), pelvis (7-12%), and thorax (9-11%).[10–12] STS generally presents as a painless slowly growing mass, although pain is noted at presentation in up to one-third of cases. Red flags are (rapid) growth of a pre-existing or new mass, a diameter of more than 5 cm and invasion of deep body fascia. For the assessment of a tumour, a magnetic resonance imaging (MRI) and/or spiral CT is necessary to evaluate size and relationship of the lesion to adjacent structures.[13–15] A core needle biopsy to determine histologic type and grade of the tumour is required to obtain pre-operative diagnosis as the various subtypes differ in their prognosis and treatment protocol.[12,16,17] A Fine Needle Aspiration (FNA) is not the recommended technique for the initial diagnostic evaluation of a suspicious soft tissue mass due to its lower diagnostic accuracy, and is only useful in patients with a previous history of a malignancy to confirm a disease recurrence.

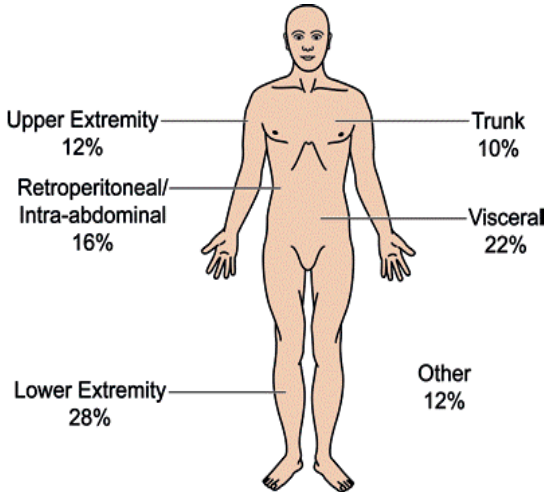


Figure 2. Locations of STS
Figure adopted from Brennan et al.[4,5]

The prognosis of STS can be relatively poor, even with intensive multimodality treatment. Survival is highly correlated with tumour stage (including tumour size, depth, lymph node involvement, distant metastases, and histologic grade), with reported 5-year overall survival rates for stages I, II and III being 90%, 81%, and 56%, respectively. The most common reason for poor prognosis is delayed diagnosis resulting in advanced disease and/or metastasis at presentation. Other important predictors of

survival are tumour location, presence of positive surgical margins, local recurrence or distant metastases at presentation.[18–21]

Treatment of STS

Evaluation and treatment of STS should be performed in a specialised, high-volume centre with a multidisciplinary sarcoma team, as this has been shown e.g. to improve the limb salvage- local control and disease free survival rates.[22–25] Treatment aims to achieve long-term survival, avoid local recurrence, maximise function and minimize short and long term treatment related morbidity. A precise balance between adequate resection margins and preservation of function is required to confer the best oncologic outcomes.[26]

Surgery remains the mainstay of, and the only curative treatment for STS. In order to minimize the chance of a local recurrence, a resection margin of 1.5-2.5 centimeters of healthy tissue around the resected tumour is needed. This often requires extensive resections, which necessitated amputation in the past.[27,28] In the 1980s however, comparable disease-free and overall survival rates were shown for patients with extremity STS (ESTS) treated with limb-sparing resection combined with radiotherapy (RT) compared to an amputation.[29–32] Limb-sparing treatment protocols combining surgery and radiotherapy have since become the gold standard in the treatment of patients with ESTS. Chemotherapy has limited clinical benefit and is therefore only considered in specific subtypes of STS that predominantly occur in children (e.g. rhabdomyosarcoma, Ewing sarcoma and osteogenic sarcoma).[33–37]

Improvements in imaging, surgical techniques, adjuvant therapies and increased experience have now made limb preservation possible in almost 90% of limb sarcomas, without increasing the risk of local recurrence.[11,38] This can result in extensive soft tissue defects that cannot be managed using simple wound closure or skin grafting techniques. This holds especially true in the distal parts of the extremities where soft tissues are scarce and local rearrangement of tissue is difficult or impossible. Reconstructive surgery plays an essential role in these extensive ESTS resections, as it provides wound closure and coverage for vital structures or prostheses while maximizing functional outcomes.[39,40]

Reconstructive surgery

STS resections frequently result in large defects that require reconstructive procedures. Reconstructive surgery, in its broadest sense, means the use of surgery to restore the

original appearance, functionality and mobility of certain body parts after they have been destroyed by illness or trauma. Reconstructive surgery is often required to repair blood vessels, nerves, muscles or bone in large defects as well. Furthermore, when there is lack of tissue to achieve primary wound closure or to cover critical structures (i.e. nerves, tendons, joints or orthopedic hardware), reconstructive surgery provides tissues to enable adequate coverage for a wound. The transfer of vascularized tissue to a defect is thought to promote wound healing by reducing dead space, decrease of tension on the wound and improved vascularization.

The principle of soft tissue reconstruction is based on the reconstructive ladder, in which treatment options increase in complexity (Table 1).[41,42] Surgeons previously attempted to use the most simple and safe method possible, whereby healing by secondary intention was considered as first choice and free tissue transfer being the most technically challenging technique as last. Nowadays, surgeons select the most suitable technique providing the best functionality and form according to the reconstructive elevator principle.[43]

TABLE 1

The reconstructive ladder

Reconstructive method	
Free flap	↑ More complex
Regional flap	
Local flap	
Skin graft	↓ Less complex
Secondary closure	
Direct closure	

Skin grafts

A skin graft is the transfer of a very thin sheet of skin, without an own blood supply, harvested from a distant donor site and transferred to a defect. The tissue survives by a process called plasmatic imbibition, which is the absorbance of transudate from the recipient site supplying oxygen to the graft until it has developed new blood vessels through angioneogenesis. This technique is only possible if the recipient site contains well vascularized tissue to facilitate graft survival.[44,45]

Flaps

Flaps are tissue transfers that can consist of multiple types of tissue, e.g. skin,

muscle, nerve, fascia and bone. The tissue can either be elevated on its blood supply as a local or regional pedicled flap, without detaching the supplying blood vessels and transpositioned into the defect or it can be harvested as a free flap often from a distant area of the body by disconnecting it's blood supply and reconnecting it to the blood supply at the defect.[42]

Flap choice is determined by the site and size of the defect and the availability of local tissues. Local or pedicled flaps are usually the preferred method for reconstruction of small to midsize defects where direct closure or skin grafts are not feasible. However, these flaps can be tricky in the limbs, especially in the distal extremities where the availability of soft tissue for reconstruction can be scarce. Moreover, since pre-operative radiation therapy is more frequently used in the current treatment of STS, pedicled flaps are often located within the irradiated field.

When local or pedicled soft tissue flaps are unavailable or insufficient, reconstruction with a free flap is required. Free flaps have their blood flow restored at the recipient site through microvascular anastomosis of the blood vessels. This allows covering defects with very large areas of well-vascularized tissue, unaffected by radiation. Free flaps are often perceived to be technically more challenging with extended operation times and therefore higher risk of complications.

The majority of the STS patients can now be expected to survive for several years after their initial operation. There has been a shift of focus towards preservation or restoration of function. Advanced reconstructive methods are more often used nowadays to aim for superior results even when simpler options are available.[46,47] This choice however is often based on a surgeon's clinical experience, since there is no clear guideline for this in the current literature. More importantly, it is unclear what the exact effect is of the increased use of these extensive reconstructive procedures on the post-operative course of STS patients.

Treatment morbidity

While the management of STS has considerably evolved in the past years, post-operative wound complications (WC) remain an important source of morbidity.[48–51] The most common complications include cellulitis, abscess formation, wound dehiscence, seroma, hematoma, wound necrosis and vascular flap compromise, occurring in 16 up to 56 percent of the patients. These WC may require ongoing management with vacuum-assisted closure (VAC), prolonged deep wound packing or a re-operation,

often delaying a patient's rehabilitation and potentially negatively influencing their functional outcomes.[52–54] Although the exact cause of wound healing complications is not well understood, it is known that it is multifactorial. The systematic review in this thesis gives an overview of all known predictors of complications in the treatment of STS up to now.

A correct risk assessment of complications based on specific patient, tumour and treatment factors is required in order to provide optimal patient care, and to inform patients about the risks of a surgical procedure during pre-operative consultation

ACS NSQIP surgical risk calculator

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) developed a surgical risk calculator, which is published online and openly accessible. The risk calculator tries to predict the chance for a patient to develop any of nine different, most common complications within 30 days after surgery, by taking into account the proposed surgical procedure and 21 patient characteristics.[55–57] An example of the risk calculator and an overview of the characteristics and comorbidities are listed in Figure 3 and Figure 4. The tool has been developed using data from The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®) database, which contains validated data on patient demographics, co-morbidities and 30-day post-operative outcomes. This data has been compiled in a standardized manner from more than 200 participating hospital(s) in the United States and contains more than one million patients who have undergone a wide range of surgical procedures. By using these data to develop the universal risk calculator, they have generated a customized risk assessment for more than 1500 individual surgical procedures. A tool that is universal, user-friendly and provides a correct estimation of a patient's risk of developing complications in a wide range of surgical procedures seems to be a valuable addition to the pre-operative decision making process.

At this moment, the NSQIP surgical risk calculator is available to everybody including patients who underwent or are scheduled for reconstructive surgery. However, its value has never actually been validated for patients who underwent reconstructive surgery.

Content of this thesis

This thesis addresses the role of reconstructive surgery in the surgical management of soft tissue sarcomas and the influence on post-operative complications. The aims of the present thesis are to:

- Describe complications and re-operation rates in the surgical treatment of STS
- Provide an overview of the risk factors for post-operative complications in STStreatment
- Evaluate the validity of the ACS NSQIP surgical risk calculator for patients requiring flap reconstruction following STS resection
- Investigate the impact of flap reconstructions on post-operative complications after STS resection
- Evaluate the risk factors for complications in patients requiring flap reconstruction following STS resection
- Discover if there is a difference in complications and long-term functional results between free and pedicled flap reconstructions following STS resection

The final chapters of this thesis provide a summary of the results and describe future perspectives of STS treatment.

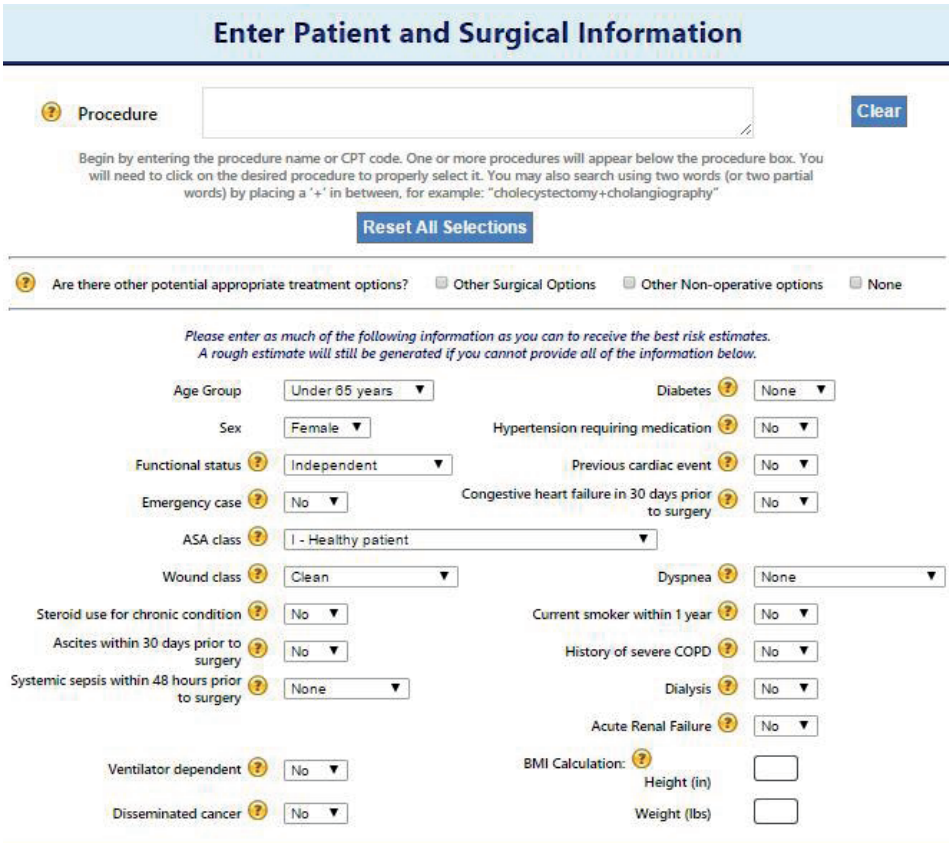


Figure 3. ACS NSQIP Surgical Risk Calculator: patient demographics and medical comorbidities

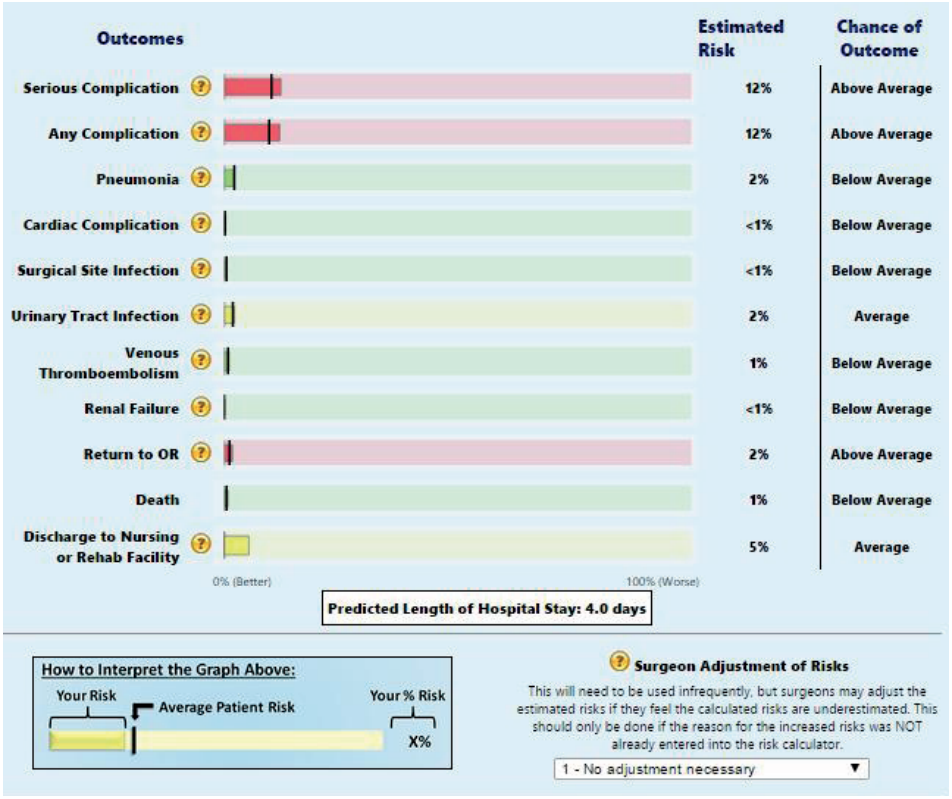


Figure 4. ACS NSQIP Surgical Risk Calculator: the outcomes

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CHAPTER 2

Risk factors for post-operative wound complications after extremity soft tissue sarcoma resection — A systematic review and meta-analyses

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Submitted

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 re-operation 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 thirteen studies included, there was an overall wound complication rate of 28.3% (95% CI 24.29-32.34) and re-operation rate of 13.78% (95% CI 10.79-16.78) in 2570 patients. Individual studies reported that older patient age, obesity, smoking, diabetes, large tumour size, tumour site and pre-operative radiotherapy were associated with adverse outcomes. Tumours of the lower limb, diabetes 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.

Conclusion: Despite advancements in the treatment of ESTS, post-operative complication rates remain high. Awareness of the risk factors for wound complications especially those that may be modifiable is essential to decrease post-operative morbidities in these patients in order to improve treatment outcomes and quality of life.

Key Words: Soft tissue sarcoma, complications, risk factors

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 tumours are now considered resectable the complexity of soft tissue sarcoma surgery has increased and consequently it might be expected that more patients would experience post-operative 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 pre-operative radiation means that these patients are at particularly high risk for post-operative 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 pre-operatively. 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 post-operative wound complications in the same patient group and (3) to investigate whether meta-analysis of the results was possible in order to establish pooled estimates of the wound complication rates, re-operation 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 post-operative 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, Post-operative Complications]. Concepts commonly related to these keywords were also usedFor 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) post-operative complications were defined as a main outcome, and (4) multivariate analyses of risk factors for complications was 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 tumours that were initially inoperable but were

excised after treatment with neoadjuvant radiation, chemotherapy or hyperthermic isolated limb perfusion were excluded since 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 tumour, study design, objectives, inclusion and exclusion criteria. The primary outcomes of this study were the proportion of post-operative wound complications and re-operations. 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, since this overlap was not substantial, all of these studies were included in the meta-analyses on post-operative wound complications and re-operations. 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 re-operation rates with associated Odds Ratios (OR) and corresponding 95% Confidence Intervals (CI) for all risk factors were extracted and entered in a datasheet. Meta-analyses were performed for wound complications, re-operations 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 re-operation 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 tumour 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 re-operations 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. p-values <0.05 were considered to be significant.

Results

Literature search

A flowchart of the study selection is shown in Figure 1. The literature search identified a total of 7120 articles of which 1951 were found to be duplicates and were removed, which resulted in a total of 5169 unique articles for review. Two reviewers independently applied exclusion and inclusion criteria and selected 178 papers for full text review. Finally, a total of thirteen studies were included in this systematic review.

Study characteristics

Table 1 shows the characteristics of the thirteen studies included in this review. The articles were published between 1993 and 2016, reporting on a total of 2570 patients. All but one publication[11] used a retrospective study design, and the majority included extremity cases only (8 of 13 papers) but the inclusion criteria varied between studies (supplementary Table 2). Where reported, 97% of patients presented with a primary tumour (ranging from 86–100% in 11 studies), whereas 3% required excision of a local or regional recurrence (ranging from 0-14% in 11 studies).[11,13,14,26-33] The treatment modalities varied among the studies, however all treatment regimens included pre- or post-operative radiation therapy. Four studies only included pre-operatively irradiated patients,[30–32,34] while two other studies only included post-operatively radiated patients.[28,29] Excluding these six studies, the proportion of either pre- or post-operatively radiated STS patients ranged from 67-90% of the study population in the other 7 studies.[11,13,14,25–27,33] The mean percentage of patients treated with pre-operative radiation was 62% (range: 31-86%) and post-operative radiotherapy was administered in 24% of the patients (range: 4-52%) in these studies. The proportion of patients treated with chemotherapy was low (25%, ranging from 0-69%, 13 studies). Overall, 82% (range: 56-100%, 13 studies) of patients underwent primary wound closure while soft tissue reconstructive surgery was required in 18% (range: 0-44%, 13 studies) of the cases.

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

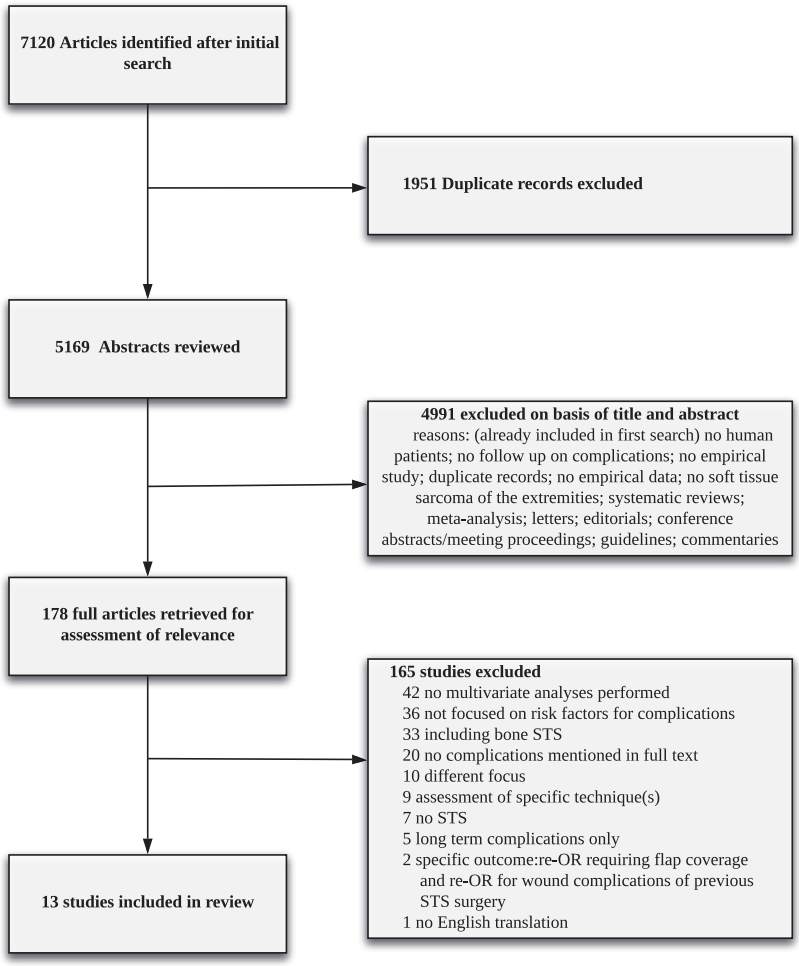


Figure 1. Diagram of literature search
Flowchart summarizing the search strategies and subsequent selection of studies for the systematic review.

Wound complications

In 2002 O'Sullivan *et al.* introduced a definition of major wound complications,[11] that has been adopted by six of the included studies.[13,14,27,30–32] Three other studies used different criteria, some of which were partly based on the definition of O'Sullivan and colleagues.[26,33,34] The remaining three studies solely reported wound complications requiring a re-operation.[25,28,29] All definitions of complications are shown in supplementary Table 2. Wound complication rates were reported in ten studies and varied from 17.6 to 36.6%. Meta-analyses identified an overall wound complication

TABLE 1

Overview characteristics included studies

Year	Authors	Study design	Center	n	Research goal	STS Site	P/LR (%)	Tumour 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 post-op RT	E	P (91%) LR (9%)	-	71.4	28.6	100 (48/52)	0	WC + LC + OS	25.8	104
2005	Alektiar[29]	RR	S	369	PC in high grade STS+ post-op RT (RT/BRT)	E	P (100%)	-	100	0	100 (post-op)	34	WC requiring re-OR + long term WC + LC + OS + DMFS	-	7.9
2006	Cannon[14]	RR	S	412	PC/RS + pre vs post-op RT	Lower E	P (100%)	# 8 cm (1.2-30)	79.6	20.4	100 (65/35)	41	WC (acute and long term)	27.4	8.5
2009	Rimner[28]	RR	S	255	PC + post-op RT (RT/BRT)	Thigh	P (100%)	-	100	0	100 (post-op)	31	WC requiring re-OR + long term WC + LC + OS + DMFS	-	9.4
2010	Davidge[26]	RR	M	247	PC vs RS +/- RT (pre/post-op)	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 post-op 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[32]	RR	S	73	PC/RS + pre-op 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/ post-op)	Thigh +pelvis	P (100%)	-	62	38	90 (86/4)	69	WC	32	-
STS location in extremity + trunk +/- head & neck															
1993	Bujko[34]	RR	S	202	PC/RS + pre-op RT +/- post-op RT	E+T+H	P (86%) LR (14%)	-	89	11	100 (100/71)	24	WC	36.6	16.5
1994	Peat[25]	RR	S	180	PC vs RS +/- RT (pre-/ post-op)	E+T	-	#90cm2	76	24	- (31/ -)	18	WC requiring re-OR + LC	-	16
2013	Baldini[31]	RR	M	103	PC/RS + pre-op RT	E+T	P (91%) LR (9%)	# 8.4 cm (2-25)	70	30	100 (pre-op)	18	WC	35	25.2
2014	Moore[33]	RR	S	256	PC/RS +/- RT (pre/ post-op)	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 + pre-op RT	E+T	P (100%)	-	56	44	100 (pre-op)	38	WC	25	23.9

Abbreviations: RR: retrospective review, RCT: randomized controlled trial, S: single center, M: multi center, PC: primary closure RS: reconstructive surgery RT: radiotherapy, BRT: brachyradiotherapy, E:Extremities (both upper and lower), T:trunk, H:Head&neck, P: primary tumour, LR: Local recurrence, LC: local control, OS: overall survival, DMFS: distant metastasis free survival, FS: functional status, WC: wound complication, re-OR: re-operation; pre-op: pre-operative; post-op: post-operative

*total study population: 309 but separate analyses for 130 patient s with only extremity + surgery without neoadjucant chemotherapy was performed. Results in this table are based on this group.

rate of 28.31% (95% CI 24.29-32.34, 10 studies[11,13,14,26,27,30–34]) with high heterogeneity (I^2 71%, Figure 2). Sub-analyses of the studies stratified for tumour location showed an overall wound complication rate of 27.70% (95% CI 25.08-30.33, I^2 0.0%, 6 studies[11,13,14,26,27,32]) in the extremity only studies and 28.30% (95% CI 17.97-38.63, I^2 88.43%, 4 studies[30,31,33,34]) in those including STS located in the extremity, as well as the trunk and head & neck.

Re-operations

The re-operation rate was reported in eleven studies and ranged from 7.86 to 25.24%. Meta-analyses of these rates are displayed in Figure 2, and show an overall re-operation rate of 13.78% (95% CI 10.79-16.78, 11 studies[11,13,14,25,26,28–32,34]). However, due to high statistical heterogeneity (I^2 78%), stratification on tumour location was performed. This resulted in lower heterogeneity with a re-operation rate of 10.48% (95% CI 8.11-12.86, I^2 58.29%, 7 studies[11,13,14,26,28,29,32]) in the extremity only group and a slightly higher re-operation rate of 19.28% (95% CI 14.85-23.71, I^2 44.60%, 4 studies[25,30,31,34]) in the studies including extremity, trunk and head & neck STS.

Risk factors for complications

All recorded risk factors for wound complications and their associated odds ratios (OR) are presented in Table 2. In order 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, but 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% Confidence Interval (CI)) in uni- or multivariate analysis were subsequently included in the meta-analyses. Where possible the results of multivariate meta-analysis are reported below. In cases where multivariate data was 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 re-operations was insufficient to perform meta-analyses.

Age

Age was evaluated in all but two publications[13,29] and was included in the multivariate analyses of six studies. In univariate analysis, age was significant in two studies[28,34] and not significant in six publications[25,27,31–33,35] Three publications did not report on

their univariate findings.[11,14,26] In multivariate analyses, older age was found to be an independent predictor for wound complications or re-operations in three of six studies.[26,28,34] Age was not found to be significantly associated with complications in multivariate analyses of the remaining three studies.[11,14,27] However, pooling of these results was not feasible due to either incomplete data or the use of different cut-off points (e.g. 50 years, 60 years, or as a continuous variable).

Smoking

The effect of smoking was evaluated by univariate analyses in six studies[25,27,30–33] and subsequently included in multivariate analyses of four.[25,27,31,33] Two of these studies showed a significant effect of smoking on wound complications on both univariate- and multivariate analyses.[31,33] Peat *et al.* reported a significant effect of smoking on re-operation 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 analyses[32] and the two remaining studies found no significant effect of smoking on complications.[27,30] Due to missing data, the univariate OR of only three studies[31–33] were pooled with an overall OR of 2.56 (95% CI 1.45-4.53, I^2 0%, Figure 3).

Obesity

BMI was included in univariate analyses in six studies[27,30–34] and multivariate analyses in two of these.[27,33] By univariate analyses, obesity was not significantly related to wound complications in three studies.[30–32] Moore *et al.* reported a significant effect of obesity in both univariate and multivariate analyses,[33] 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 re-operation rates in univariate analyses.[34] 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. Three studies[27,33,34] were suitable for pooling, and demonstrated an overall univariate OR of 1.45 (95% CI 0.78-2.72, I^2 37%, Figure 3).

Diabetes

The effect of diabetes was evaluated in univariate analyses in seven studies[25,27,30–34] and in multivariate analyses in four of these.[25,27,31,33] 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] Four reports did not find any significant effect on univariate testing.[27,30,32,34] Bujko *et al.* and Peat *et al.* grouped diabetes together with cardiovascular diseases, making them unsuitable for pooling with the other studies.[25,34] Two studies were not pooled due to missing information.[27,30]

TABLE 2

Overview of all included risk factors and Odds Ratio's (OR) for complications and re-operations

Study	n	Outcome	Patient/tumour factor	Odds Ratio (OR)		Treatment factor	Odds Ratio (OR)	
				UVA	MVA		UVA	MVA
STS location in extremity								
O'Sullivan[11]	182	WC	Age (continous)	NR	ns	Reconstructive surgery	0,94	ns
2002			Gender	NR	ns	Pre- vs. post-operative RT	2.60*	3.08*
			Pre-sentation (first/recurrence)	NR	ns			
			Tumour size > 10cm	s	1.11*			
			Prior incomplete resection	NR	ns			
			Lower extremity location	16.7*	10.4*			
Alektiar[29]	369	Re-OR	Lower extremity location	12.48*	NR*			
2005								
Cannon[14]	412	WC	Age (continous)	NR	ns	Reconstructive surgery	1,51	
2006			Tumour size >5 cm	2.21*	s*	Vascular reconstruction	NR	ns
						Bone exposure	NR	ns
						Periostal stripping	NR	ns
						Pre- vs. post-operative RT	2.67*	s*
Rimner[28]	255	Re-OR	Age >50	2.76*	s*	Vessel resection	2.97*	s*
2009			Gender	ns	ns	Post-operative chemotherapy	ns	
			Tumour size >10 cm	ns	ns	RT type (EBRT vs BRT)	s*	s*
			Thigh compartment location^	3.19*	ns			
Davidge[26]	247	WC[1] &	Age (continous)	NR	1.02[1]*	Reconstructive surgery	1.52[1]/1.72[2]	0.78[1]
2010		Re-OR[2]	Prior incomplete resection	NR	0.84[1]	Bone resection	NR	4.06[1]*
			Tumour size (continous)	NR	1.08[1]*	Pre-operative RT	NR	2.67[1]*
			Tumour stage 3	NR	1.28[1]			
Korah[13]	118	WC[1] &	Tumour size >8cm	NR	s[1]*	Pre- vs. post-operative RT	s[1] ?[2]*	s[1]*
2012		Re-OR[2]	Lower extremity location	1.29[1]*/2.85[2]*	s[1] ?[2]*			

Rosenberg[32]	73	WC[1] &	Age (continous)	ns[1] ?[2]		Reconstructive surgery	1.41[1]/0.67[2]	
2013		Re-OR[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]		Pre-operative 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]*
			Tumour size (continous)	1.074[1]*/1.02[2]	NR			
			High tumour 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]		WC	Age ≥50	ns		Reconstructive surgery	s	ns
2013	84	Extremity	Smoking	s	10.06*			
		group	Tumour size >10 cm	s	3.3*			
			Tumour proximity (<3mm to skin)	s	6.8*			
			Lower extremity location	2,19				
	103	Total	Age ≥50	ns		Reconstructive surgery	2.77*	6.4*
		popula-tion	Smoking	3,21				
			Obesity	ns				
			Diabetes	4.5*	5.6*			
			Tumour size >10 cm	2.94*	6.2*			
			Tumour proximity (<3mm to skin)	3.9*	3.9*			
Ziegele[27]	81	WC	Age (continous)	ns	ns	Reconstructive surgery	2,34	3.69*
2016			Smoking	ns	ns	Pre-operative chemotherapy	1,18	ns
			BMI > 28.8	1,53	ns	Pre-operative RT	ns	ns
			Diabetes	ns	ns			
			Tumour size ≥10 cm	2,11				
			Tumour volume ≥228.1 mL	1.001*	1.001*			
			High tumour grade	ns				
			Tumour proximity (<3mm to skin)	ns	ns			

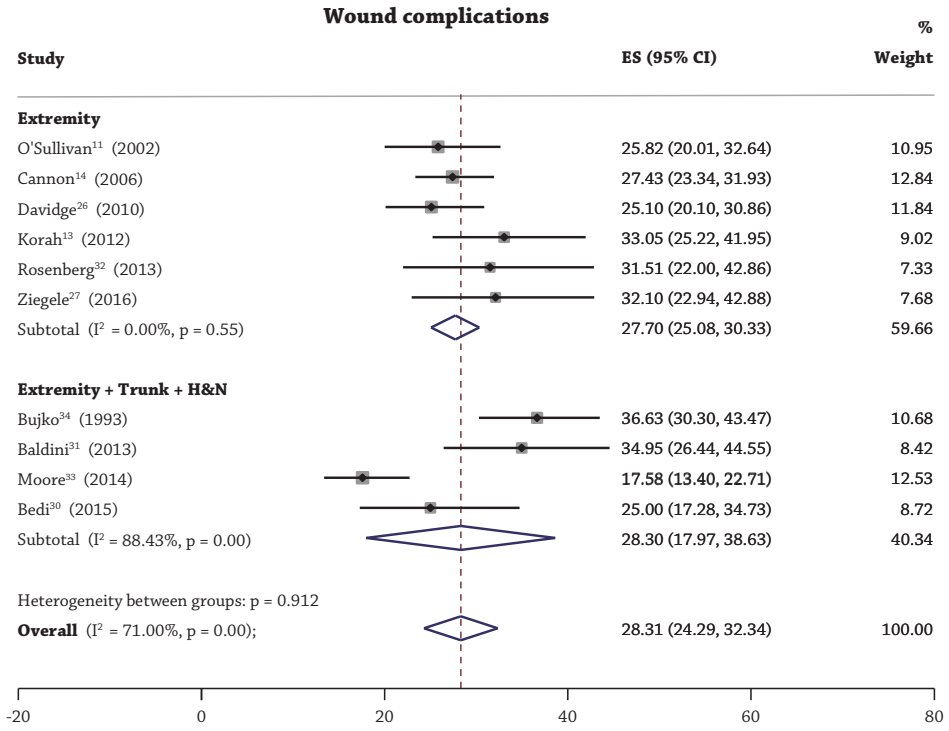
- Table 2 continued -

Study	n	Outcome	Patient/tumour factor	Odds Ratio (OR)		Treatment factor	Odds Ratio (OR)	
				UVA	MVA		UVA	MVA
STS location in extremity + trunk +/- head & neck								
Bujko[34]	202	WC[1] &	Age ≥60	1.94[1]*/1.73[2]		Post-operative chemotherapy	0.73[1]/0.41[2]	
1993		Re-OR[2]	Age (continous)	s[1] ?[2]*	1.00[1]*	Post-operative RT boost	ns[1] ?[2]	
			Female gender	0.61[1]/0.47[2]		Pre-operative RT dose	ns[1] ?[2]	
			Obesity	0.87[1]/1.03[2]		2 fractions pre-op RT/day	1.94[1]*/1.52[2]	1.84[1]*
			Diabetes or cardiovacular disease	1.39[1]/1.04[2]		Time interval pre-op RT	ns[1] ?[2]	
			Pre-sentation (first/recurrence)	1.34[1]/1.26[2]		Blood loss ≥1000 ml	3.12[1]*/2.04[2]	2.94[1]*
			Tumour size ≥10cm	1.28[1]/1.08[2]	ns[1]			
			High tumour 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	Pre-operative RT	3.34*	s
			Diabetes or cardiovascular disease	4.68*	ns			
			Tumour volume >100 cm^2	6.94*	s			
			Lower extremity location	1,19				
Moore[33]	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*	Pre-operative RT	2.3*	2.46*
			Diabetes	4.71*	4.07*	RT dose	ns	
			Cardiovascular disease	s	ns	Time interval pre-op RT	ns	
			Hypercholesterolemia	s	ns			
			Tumour size >10 cm	3,16				
			Tumour size (continous)	1.06*	1.05*			
			Tumour depth	2,62	ns			
			High tumour 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		Pre-operative chemotherapy	ns	
			Diabetes	ns		Vascular resection	s	ns
			Cardiovascular disease	ns		Time interval pre-op RT	ns	
			Tumour size (continous)	ns		Biopsy outside institution	3.33*	5.79*
			Tumour depth	ns				
			High tumour grade	ns				
			Lower extremity location	s	16.66*			

Abbreviations: UVA:univariate analyses; MVA:multivariate analyses; 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; *denotes statistical significance ^Medial/posterior thigh compartment vs. anterior compartment

[1]:risk factor for wound complications [2]:risk factor for requiring a re-OR.



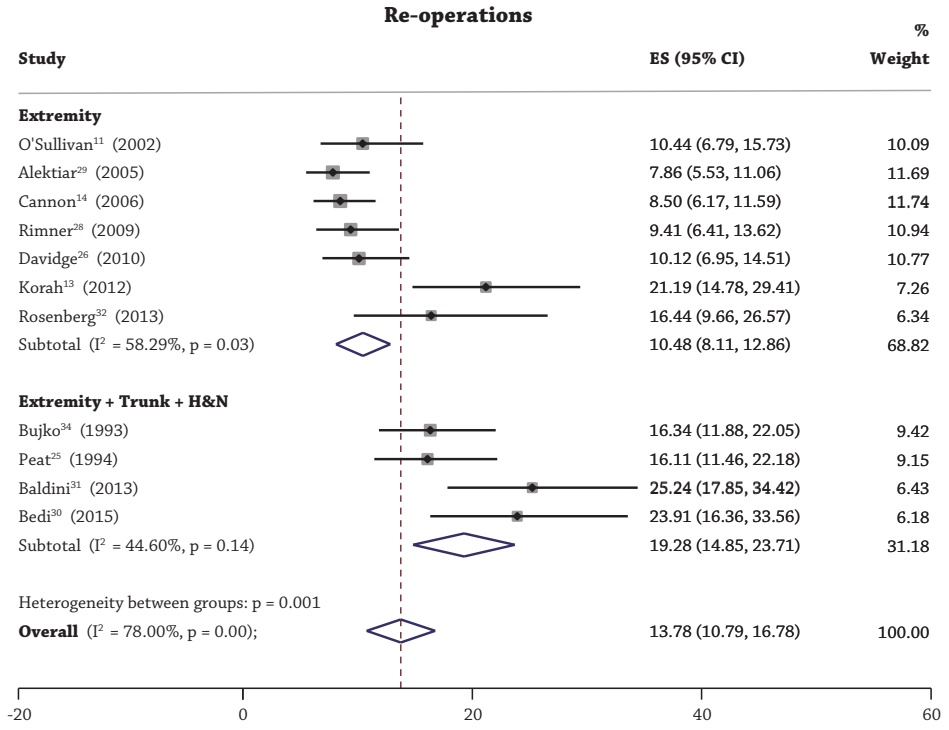


Figure 2. Pooled wound complication and re-operation rates
ES: effect size; CI: confidence interval; I^2 : degree of heterogeneity; H&N: head and neck

Pooled analyses in Figure 3 shows an overall multivariate OR of 4.49 (95% CI 1.91-10.58, I^2 0%, 2 studies,[31,33] Figure 3).

Tumour size

All but one author[29] evaluated tumour size in univariate analyses and subsequently included this factor in multivariate analyses (Table 2). Even though various cut-off points were used (5, 8 or 10 cm, and size as a continuous variable or as a measure of volume), tumour size was a significant independent predictor for either wound complications or re-operations in multivariate analyses in eight of twelve studies.[11,13,14,25–27,31,33] Studies using similar cut-off points were included in meta-analyses (Figure 3). Considering tumour size as a continuous variable the overall multivariate OR was 1.06 (95% CI 1.03-1.10, I^2 0%, 2 studies[26,33]). Tumours >10 cm showed a multivariate OR of 2.40 (95% CI 0.45-12.81, 2 studies[11,31]) but with a high level of heterogeneity (I^2 89.4%, Figure 3).

Tumour grade

Tumour grade showed significance in two of five studies by univariate analyses[27,30,32–34] which then included this factor in multivariate analyses.[32,34] Rosenberg *et al.* indicated low tumour grade as a risk factor for re-operations, which remained significant in multivariate analysis.[32] Conversely Bujko *et al.* showed high tumour grade to be associated with wound complications in univariate analysis but this was not significant in multivariate testing.[34] Three studies[32–34] were included in the pooled analyses with an overall univariate OR of 1.59 (95% CI 0.42-6.02, Figure 3) and with a high level of heterogeneity (I^2 81.2%).

Tumour location

Tumour location was analyzed in all but three reports,[14,26,27] 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 compared to 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 compared to the upper extremity or head and neck locations.[33] The eight remaining studies analyzed the influence of lower versus upper extremity tumour location on wound complication or re-operation rates. In seven of these studies, lower extremity tumours were associated with significantly more complications or re-operations than upper extremity tumours in univariate analyses,[11,13,27,29,32–34] and this remained significant in multivariate analyses of six reports. The pooled multivariate OR was 4.84 (95% CI 1.78-13.17, I^2 25.4%, 3 studies,[11,33,35] Figure 3).

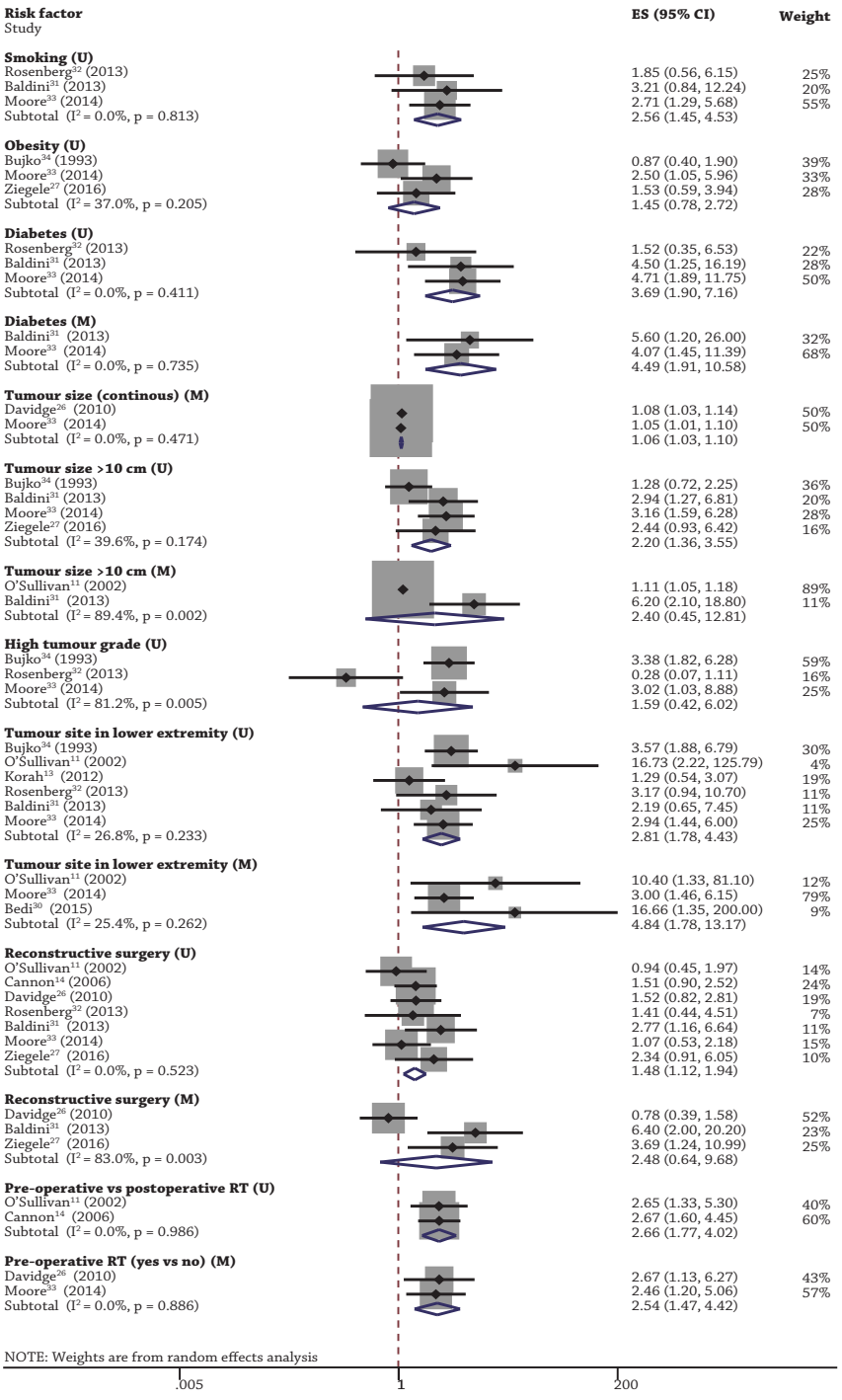


Figure 3. Pooled analyses - risk factors for complications, stratified by risk factor

ES: effect size; CI: confidence interval; U: univariate analysis; M: multivariate analysis; I^2 : degree of heterogeneity

Tumour depth

Tumour 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 two of these studies.[30,33] Baldini *et al.* reported that tumour proximity to skin surface (<3 mm) increased the wound complication rate[31] but this finding was not confirmed in others. No studies found a significant impact of tumour depth in relation to the fascia on complications. Pooling was not possible due to missing data

Flap reconstruction

The influence of soft tissue reconstructive surgery on wound complications or re-operation rates was considered by nine studies (Table 2).[11,14,25–27,30-33] One study found significantly increased complication rates following flap reconstruction in both univariate and multivariate analyses.[31] Ziegele and colleagues showed significantly more wound complications in patients undergoing flap reconstructions on multivariate analyses.[27] The seven remaining reports showed no significant differences in wound complication or re-operation rates following flap reconstructions compared to wounds closed primarily. Pooled analyses found a multivariate OR of 2.48 (95% CI 0.64-9.68, 3 studies,[26,27,31] Figure 3) but with a high level of heterogeneity (I^2 83%).

Other reconstructive surgery

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

Chemotherapy

The impact of chemotherapy on post-operative complications was evaluated in 6 studies. Chemotherapy was delivered pre-operatively,[27,30,32] post-operatively,[28,34] or both.[33] There was no significant association between chemotherapy and post-operative wound complications or re-operations, therefore no meta-analyses was performed.

Radiotherapy

All studies included radiated STS patients, ranging from 38 to 100 percent of the study populations (Table 1). Four studies included either exclusively pre-operative radiation or post-operative radiation [28–31] (Table 2) and did not evaluate the impact of radiotherapy on wound complications. Of the remaining nine studies, seven considered the influence of pre-operative radiotherapy on wound complications or re-operations

TABLE 3

Summary of the meta-analyses

Variable	Model	N	Pooled OR (95% CI)	Heterogeneity (I^2)*	p-value
Lower Limb	MVA	3	4.84 (1.78 - 13.17)	Low/moderate	0.26
Diabetes	MVA	2	4.49 (1.91 - 10.58)	Low	0.74
Radiation	MVA	2	2.54 (1.47 - 4.42)	Low	0.89
Tumour size	MVA	2	2.40 (0.45 - 12.81)	High	**0.002**
Flap Reconstruction	MVA	3	2.48 (0.64 - 9.68)	High	**0.003**
Smoking	UVA	3	2.56 (1.45 - 4.53)	Low	0.81
Obesity	UVA	3	1.45 (0.78 - 2.72)	Moderate	0.21
Tumour Grade	UVA	3	1.59 0.42 - 6.02)	High	**0.005**
Age	N/A				
Tumor Depth	N/A				
Chemotherapy	N/A				

UVA: univariate analysis; MVA: multivariate analysis; N/A: not applicable;
* I^2 : degree of heterogeneity (I^2 <25% = low; I^2 25% - 50% = moderate; I^2 >50% = high)

in both univariate and multivariate analyses. However, the reference group for pre-operative radiotherapy differed among the studies. The reference was the absence of radiation in three studies,[25,26,33] and post-operative radiation in four others.[11,13,14,27] Pre-operative radiotherapy showed a significant uni- and multivariate association with increased wound complications compared to post-operative radiotherapy in three of four reports.[11,13,14] Pooled analyses showed a univariate OR of 2.66 (95% CI 1.77-4.02, I^2 0.0%, 2 studies,[11,14] Figure 3). Multivariate testing was not performed due to incomplete data. Pre-operative radiotherapy compared to no radiotherapy also showed a significant uni- and multivariate association with increased wound complications in two studies[26,33] and with re-operations in one study.[25] Multivariate pooling showed an OR of 2.54 (95% CI 1.47-4.42, I^2 0.0%, 2 studies,[26,33] Figure 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 post-operative wound complications in this population and among those, 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 account for the development of post-operative wound complications in patients who undergo resection of ESTS.

Tumour location in the lower extremity was the strongest predictor of wound complications in this meta-analysis, and increasing the risk almost five-fold compared to lesions in the upper extremity with a relatively low level of heterogeneity between studies.[11,30,33] The definition of lower limb varied however, with some studies including tumours of the buttock or pelvis.[25,27,33,34] Diabetes was also found to be an important predictor of wound complications on meta-analysis and increased the risk of complications four-fold with very low heterogeneity between studies.

Patients who were treated with pre-operative radiation had double the risk of wound complications compared to patients who had no radiation with very low heterogeneity between studies.[26,33] The timing of radiation in the treatment of ESTS patients remains controversial. Neo-adjuvant radiation permits smaller doses and treatment fields, which limits chronic fibrosis and improves long-term functional outcomes.[36] However, as surgical resection tends to be performed relatively soon after completion of pre-operative radiation (e.g. 4-6 weeks),[37] the acute effects of radiation may adversely affect wound healing.[11,14,24] Unfortunately there was insufficient data to perform pooled multivariate analysis of pre- versus post-operative radiation in this study but 3 of the 4 studies that performed multivariate analysis reported significantly increased wound complications after neo-adjuvant treatment.[11,13,14] Pooling of univariate data also suggested pre-operative radiation significantly contributed to complications.

Tumours over 10 cm were found to have a higher risk of post-operative wound complications but with a high degree of heterogeneity between studies. However 8 of 12 studies reported a significant positive association between larger tumour size and more wound complications in their individual multivariate analyses suggesting that it is an important risk factor.[11,13,14,25–27,31,33]

There was inadequate reporting to perform pooling of multivariate data for a number of variables including smoking, obesity, and tumour grade. Of these, smoking showed a positive association with wound complications with an OR of 2.56 and a low level of heterogeneity (I^2 0%) on meta-analysis of univariate data.[31–33] Although many studies have indicated that obesity is an important risk factor for wound healing complications, this was not demonstrated in this current study, although only 3 papers were suitable

for inclusion in the univariate meta-analysis.[31–33] Tumour grade was not correlated with wound complications by univariate meta-analysis.[32–34] Age, chemotherapy and tumour depth could not be included in pooled analyses.

The contribution of flap reconstruction to post-operative complications is a matter of some debate. While flaps increase the complexity of surgery they also import well-vascularized tissue that could enhance wound healing.[18,23,38,39] The majority of included studies did not find an association between the use of flaps and complications in their individual analyses but there was inadequate reporting for pooling of multivariate data. Subsequent to initiating this review we performed a comprehensive investigation in a large series of ESTS patients and found that flaps did not increase the risk of complications.[40] Furthermore we identified that significant risk factors differed between patients who had flaps and those who did not. Tumours of the lower extremity and pre-operative radiation were only associated with complications following primary closure, suggesting that flap reconstruction can confer positive wound healing benefits in these patients. Conversely obesity and other medical comorbidities were only associated with complications following flap reconstruction.

These findings suggest that due to the heterogeneous nature of the disease, medical comorbidities and treatment not all patients can be considered collectively when assessing significant risk factors for wound complication. This is further supported by our finding that risk factors associated with upper limb tumours may differ from those in the lower limb in patients undergoing flap reconstruction.[41] In addition we identified synergistic relationships between patient and treatment related variables that may further increase the risk of complications in individual patients.[20] Continued investigation is required to understand the role of individual risk factors in particular clinical scenarios and to guide development of disease-specific risk calculators that can provide accurate and personalized pre-operative assessment for ESTS patients.[42]

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. It must also be kept in mind that due to outcome bias, significant results are generally published more frequently and the majority of studies excluded from the pooled analyses due to missing information had non-significant findings. Therefore the

pooled OR's 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 multicentre 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.

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. Although diabetes was identified as an important risk factor there was insufficient data to consider the effects of other comorbidities. We recently reported that cerebrovascular and cardiac diseases are strong predictors of complications in ESTS patients undergoing flap reconstruction.[20] In addition we only considered complications related to post-operative 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.

A small number of studies have been published since we performed this systematic review, and were therefore not included in the meta-analysis.[19–23,40] These studies similarly confirmed the high rate of post-operative complications for patients following resection of ESTS and also confirmed diabetes, radiation and lower extremity tumour locations as important contributing factors.

Conclusion

Although multimodal treatment of patients with ESTS has made surgical resection and limb preservation feasible in an increasing number of patients, post-operative wound complication rates remain high. This systematic review identifies a number of patient and tumour related variables that contribute to wound complications following resection of ESTS. The conclusions of this study are, however, limited by 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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Supplementary tables

TABLE S1

Search strategy electronic databases

Database	Search	Hits
Embase	(exp sarcoma OR soft tissue tumor OR connective tissue tumor OR sarcoma*.tw. OR adenosarcoma*.tw. OR carcinosarcoma*.tw. OR carcinoma 256.tw. OR chondrosarcoma*.tw. OR desmoplastic small round cell tumor*.tw. OR fibrosarcoma*.tw. OR dermatofibrosarcoma*.tw. OR neurofibrosarcoma*.tw. OR hemangiosarcoma*.tw. OR haemangiosarcoma*.tw. OR leiomyosarcoma*.tw. OR (malignant* adj2 histiocytoma*).tw. OR liposarcoma*.tw. OR lymphangiosarcoma*.tw. OR (mesodermal* adj2 mixed tumor*).tw. OR myosarcoma*.tw. OR rhabdomyosarcoma*.tw. OR myxosarcoma*.tw. OR myosarcoma*.tw. OR osteosarcoma*.tw. OR (phyllodes adj2 tumor*).tw. OR (connective tissue* adj2 neoplas*).tw. OR (connective tissue* adj2 tumor*).tw. OR (connective tissue* adj2 malignan*).tw. OR (connective tissue* adj2 cancer*).tw. OR (soft tissue* adj2 neoplas*).tw. OR (soft tissue* adj2 cancer*).tw. OR (soft tissue* adj2 malignan*).tw. OR (soft tissue* adj2 tumor*).tw.) AND ((exp "bones of the arm and hand") OR exp limb OR buttock*.tw. OR extremit*.tw. OR foot.tw. OR feet.tw. OR forefoot.tw. OR ankle*.tw. OR metatars*.tw. OR hallux*.tw. OR hip.tw. OR heel.tw. OR toe.tw. OR leg.tw. OR legs.tw. OR thigh.tw. OR arm.tw. OR arms.tw. OR axilla*.tw. OR elbow.tw. OR forearm.tw. OR hand.tw. OR hands.tw. OR finger*.tw. OR metacarp*.tw. OR wrist.tw. OR shoulder*.tw. OR (amputat* adj2 stump*).tw. OR limb.tw. OR limbs.tw.) AND (exp surgical technique OR exp surgery OR exp postoperative complication OR exp postoperative care OR exp intraoperative period OR exp peroperative complication OR microsurg*.mp. OR micro surg*.mp. OR ((plastic or reconstructive*) adj2 surg*).mp. OR ((postoperative or post-operative) adj2 complicat*).tw. OR ((postoperative or post-operative) adj2 advers*).tw. OR (after surg* adj2 complica*).tw. OR (after surg* adj2 adver*).tw. OR exp anesthetic recovery/ OR (surg* adj2 flap*).tw. OR ((intraoperative* or intra-operative or peroperative*) adj2 complicat*).tw. OR ((intraoperative* or intra-operative or peroperative*) adj2 adver*).tw.)	3607
MedLine	(exp Sarcoma OR exp Soft Tissue Neoplasms OR Neoplasms, Connective Tissue OR sarcoma*.tw. OR adenosarcoma*.tw. OR carcinosarcoma*.tw. OR chondrosarcoma*.tw. OR desmoplastic small round cell tumor*.tw. OR fibrosarcoma*.tw. OR dermatofibrosarcoma*.tw. OR neurofibrosarcoma*.tw. OR hemangiosarcoma*.tw. OR haemangiosarcoma*.tw. OR leiomyosarcoma*.tw. OR (malignant* adj2 histiocytoma*).tw. OR liposarcoma*.tw. OR lymphangiosarcoma*.tw. OR (mesodermal* adj2 mixed tumor*).tw. OR myosarcoma*.tw. OR rhabdomyosarcoma*.tw. OR myxosarcoma*.tw. OR myosarcoma*.tw. OR osteosarcoma*.tw. OR (phyllodes adj2 tumor*).tw. OR (connective tissue* adj2 neoplas*).tw. OR (connective tissue* adj2 tumor*).tw. OR (connective tissue* adj2 malignan*).tw. OR (connective tissue* adj2 cancer*).tw. OR (soft tissue* adj2 neoplas*).tw. OR (soft tissue* adj2 cancer*).tw. OR (soft tissue* adj2 malignan*).tw. OR (soft tissue* adj2 tumor*).tw.) AND (exp Extremities/ OR exp "Bones of Lower Extremity" OR exp "Bones of Upper Extremity" OR extremit*.tw. OR buttock*.tw. OR foot.tw. OR feet.tw. OR forefoot.tw. OR ankle*.tw. OR metatars*.tw. OR hallux*.tw. OR hip.tw. OR heel.tw. OR toe.tw. OR leg.tw. OR legs.tw. OR thigh.tw. OR arm.tw. OR arms.tw. OR axilla*.tw. OR elbow.tw. OR forearm.tw. OR hand.tw. OR hands.tw. OR finger*.tw. OR metacarp*.tw. OR wrist.tw. OR shoulder*.tw. OR (amputat* adj2 stump*).tw. OR limb.tw. OR limbs.tw.) AND (exp Surgical Procedures, Operative/ OR exp Postoperative Complications OR exp Postoperative Care OR exp Postoperative Period OR exp Specialties, Surgical OR exp Surgical Flaps OR exp Anesthesia Recovery Period OR exp Intraoperative Complications OR microsurg*.mp. OR micro surg*.mp. OR ((plastic or reconstructive*) adj2 surg*).mp. OR ((postoperative or post-operative) adj2 complicat*).tw. OR ((postoperative or post-operative) adj2 advers*).tw. OR (after surg* adj2 complica*).tw. OR (after surg* adj2 adver*).tw.	3074

TABLE S2

Overview of inclusion and exclusion criteria of the included studies

Author	Title	Definition complication	Exclusion criteria
STS location in extremity			
O'Sullivan[11]	Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial	Standardized definition for complications*	Previous chemo or chemo needed, previous RT, age<16, presence of regional/distant metastasis, previous/concurrent malignant disease
Alektiar[29]	Influence of site on the therapeutic ratio of adjuvant radiotherapy in soft-tissue sarcoma of the extremity	Need for re-OR < 5 years Also edema, joint stiffness, nerve damage, joint stiffness and bone fractures were recorded but data not used in this review since these are long term complications.	Amputation, recurrent tumors, low-grade histologic features, distant metastasis at presentation, surgery or RT outside the participating hospital
Cannon[14]	Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas	Postoperative WC < 3 months. Categorized in: Mild: no intervention/alteration in care required Moderate: intervention/alteration required, no OR Severe: re-OR required The "moderate" and " severe" complications corresponded to the standardized definition of complications*	Amputations, recurrent tumors, definitive surgery or radiation performed outside of our institution, Pelvis and iliac fossa tumors
Rimner [28]	Influence of compartmental involvement on the patterns of morbidity in soft tissue sarcoma of the thigh	Need for re-OR < 5 years Also edema, joint stiffness, nerve damage and bone fractures were recorded but data not used in this review since these are long term complications.	Amputation, distant metastasis, treatment outside research hospital
Davidge[26]	Function and health status outcomes following soft tissue reconstruction for limb preservation in extremity soft tissue sarcoma	Any surgical complication requiring an interventional procedure (i.e., needle aspiration, incision and drainage, reoperation), any wound complication requiring deep packing for longer than 4 weeks, or any neurologic complication involving new motor deficits.	Age<16, concurrent malignancy, metastatic disease at presentation, receiving chemotherapy, atypical soft tissue sarcomas, including aggressive fibromatosis, grade 1 liposarcoma, soft tissue osteosarcoma, Ewing's soft tissue sarcoma, embryonal rhabdomyosarcoma, primitive neuroectodermal tumor, dermatofibrosarcoma protuberans, and tumors of underdetermined malignant potential.

-Table S2 continued-

Author	Title	Definition complication	Exclusion criteria
Korah[13]	Anatomic tumor location influences the success of contemporary limb-sparing surgery and radiation among adults with soft tissue sarcomas of the extremities	Standardized definition for complications*	Patients with distant metastasis at presentation, palliative doses(<40 Gy) of RT, age<16, histologic subtypes: Ewing's, osteosarcoma, chondrosarcoma, dermatofibrosarcoma protuberans,desmoids.
Rosenberg[32]	Wound complications in preoperatively irradiated soft-tissue sarcomas of the extremities	Standardized definition for complications*	Age<18, Rhabdomyosarcoma, Ewing sarcoma, and dermatifibrosarcoma protuberans
Ziegele[27]	Tumor volume is a better predictor of post-operative wound complications compared to tumor size in soft tissue sarcomas of the proximal lower extremity	Standardized definition for complications*	Amputation, metastatic disease, recurrent or non-oncologic resection of sarcomas on presentation, age <18, small subcutaneous tumors, follow-up < 6 months, peritoneal and retroperitoneal tumours, rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor, Kaposi's sarcoma, angiosarcoma, and desmoid fibromatosis
STS location in extremity + trunk +/- head & neck			
Bujko[34]	Wound healing after preoperative radiation for sarcoma of soft tissues	Any WC; wound dehiscence,infection, seroma, skin graft breakdown, hematoma. Severe WC: wound problems requiring secondary operation	Amputations
Peat[25]	Wound-healing complications after soft-tissue sarcoma surgery	Need for re-OR	Unresectable tumors, primary amputations
Baldini[31]	Predictors for major wound complications following preoperative radiotherapy and surgery for soft-tissue sarcoma of the extremities and trunk: importance of tumor proximity to skin surface	Standardized definition for complications*	Previous RT to the anatomic region of interest, age<18

Moore[33]	Major wound complication risk factors following soft tissue sarcoma resection	Major WC: any WC requiring debridement and negative pressure therapy (NPT), or a surgical intervention for wound repair, such as debridement, drainage of seroma or hematoma, or secondary wound closure. Patients with wound complications requiring deep persistent packing, as defined by O'Sullivan* were all treated with debridement and negative pressure therapy, and were consequently included within the major complications group. Cases of intravenous antibiotic therapy alone were not included.	Not stated
Bedi[30]	Biopsies in the Community Lead to Postoperative Complications in Soft Tissue Sarcomas	Standardized definition for complications* Also graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**	Metastatic disease, age< 18, recurrent sarcomas , small subcutaneous tumors, no preoperative radiation or patients who underwent postoperative radiation, rhabdomyosarcoma, extra- osseous primitive neuroectodermal tumor, Kaposi's sarcoma, angiosarcoma, and aggressive fibromatosis, follow-up of < 6 months.

WC: wound complication; OR: operation

* Studies with the same definition of complications: major WC: a secondary operation under general or regional anaesthesia for wound repair (debridement, operative drainage, and secondary wound closure including rotationplasty, free flaps, or skin grafts), or wound management without secondary operation. Wound management included an invasive procedure without general or regional anaesthesia (aspiration of seroma/hematoma,infected wound collestion, use of VAC), readmission for wound care such as intravenous antibiotics, or persistent deep packing for 120 days or longer, as defined by O'Sullivan *et al.*[11]

** Common Terminology Criteria for Adverse Events, Version 4.0 - Wound Complications: grade 1: Incisional separation of ≤25% of wound; no deeper than superficial fascia; grade 2: Incisional separation of >25% of wound; local care indicated; grade 3: Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated; grade 4: Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated; grade 5: Death (Data from the US Department of Health and Human Services).

CHAPTER 3

Can the ACS-NSQIP Surgical Risk Calculator predict post-operative complications in patients undergoing flap reconstruction following soft tissue sarcoma resection?

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Abstract

Introduction: The ACS-NSQIP surgical risk calculator is an open-access online tool that estimates the risk of adverse post-operative outcomes for a wide range of surgical procedures. Wide surgical resection of soft tissue sarcoma (STS) often requires complex reconstructive procedures that can be associated with relatively high rates of complications. This study evaluates the ability of this calculator to identify patients with STS at risk for post-operative complications following flap reconstruction.

Methods: Clinical details of 265 patients who underwent flap reconstruction following STS resection were entered into the online calculator. The predicted rates of complications were compared to the observed rates. The calculator model was validated using measures of prediction and discrimination.

Results: The mean predicted rate of any complication was 15.35 ± 5.6% which differed significantly from the observed rate of 32.5% ($p=0.009$). The c-statistic was relatively low at 0.626 indicating poor discrimination between patients who are at risk of complications and those who are not. The Brier's score of 0.242 was significantly different from 0 ($p<0.001$) indicating poor correlation between the predicted and actual probability of complications.

Conclusion: The ACS-NSQIP universal risk calculator did not maintain its predictive value in patients undergoing flap reconstruction following STS resection.

Key Words: Soft tissue sarcoma, flap reconstruction, risk calculation

Introduction

Wide surgical resection is the mainstay of treatment for most patients with soft tissue sarcomas (STS) and in many cases the resulting defect will require reconstruction. Plastic surgery is an essential part of the multi-disciplinary management of STS and improvements in reconstructive techniques have greatly extended the feasibility of extensive and curative resections.[1,2] Pedicled flaps or microvascular free tissue transfer may be necessary to achieve closure or coverage of vital structures including bones, joints, neurovascular bundles and prosthetic devices. In the case of extremity STS, flap reconstruction plays a critical role in facilitating limb salvage and preservation of function.[3, 4] Although advances in reconstructive techniques have made extensive resections possible, these complex reconstructions involve long operative procedures, extended hospital stays and protracted post-operative recovery and carry the associated risk of donor site morbidity.[5-7] While radical surgical resection and reconstruction offers a high chance of cure, limb salvage and functional recovery other treatment options including amputation may be associated with significantly lower morbidity rates. It is therefore critical that patients understand the risks associated with these complex procedures.

Quality assurance in surgery places increasing emphasis on the provision of information and involvement of the patient in the decision making process.[8-10] Traditionally patients are presented with a risk estimation based on published data and the surgeon's personal experience but the importance of including patient specific risk assessment in the pre-operative informed consent process is widely recognized.[11,12] The Institute of Medicine has identified the provision of information on treatment benefits and harm as a key priority in the delivery of high quality cancer care.[13]

The American College of Surgeons National Surgical Improvement Program (ACS-NSQIP) collects high quality validated data on patient demographics, comorbidities and 30-day post-operative complications. This data has been compiled in a standardized manner from more than 500 hospitals and comprises information on more than one million patients who have undergone a wide range of surgical procedures.[14,15] This database has been used to develop a universal risk calculator that generates a customized risk assessment for more than 1,500 individual surgical procedures.[16-18] The ACS-NSQIP surgical risk calculator is an open access online tool available to both surgeons and patients that uses 21 patient-specific variables combined with a single CPT code to deliver a personalized risk prediction for 11 adverse post-operative outcomes for that

particular surgical procedure. It is recognized as a potentially valuable addition to pre-operative consultations with the Centers for Medicare and Medicaid Services providing financial incentives to physicians who use the calculator and document discussion of the results with their patients.[19]

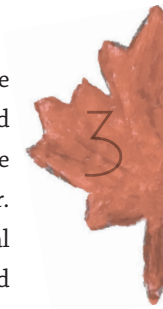
A universal risk calculator that can provide accurate and personalized risk estimation for multiple surgical procedures would be a very useful addition to the pre-operative planning and consent process. It seems unlikely, however that a single risk assessment tool that uses a standardized set of parameters would be able to effectively determine the risk of complications for a diverse range of surgical procedures. The calculator was developed and subsequently validated using data from colorectal procedures and its validity in other patient groups has not been clearly established. The aim of this study was to evaluate the accuracy of the ACS-NSQIP surgical risk calculator in sarcoma patients undergoing flap reconstruction of soft tissue defects. We hypothesize that this universal calculator may not be able to identify individuals at risk of complications in this patient group. We specifically examine the calculator's ability to predict the rate of complications in this patient population and to identify the individual patients who are at risk of developing post-operative complications.

Methods

Institutional Research Ethics Board approval was obtained for this study. Patients who underwent resection of a soft tissue sarcoma from the extremities or trunk and required reconstruction with either a pedicled or free flap between January 2006 and January 2015 were identified from a prospectively maintained institutional database at Mount Sinai Hospital, Toronto, Canada. Data was collected for the 21 pre-operative factors used by the calculator for risk prediction. These include patient demographics (age, sex, weight, height, functional status and smoking status), comorbidities (American Society of Anesthesiologists (ASA) score, hypertension, diabetes, congestive heart failure, cardiac event, dyspnea, ascites, steroid use, chronic obstructive pulmonary disease, dialysis, renal failure, systemic sepsis, ventilator dependence and disseminated cancer) and the nature of the procedure (CPT code, emergency or elective procedure, clean or contaminated).

The calculator includes five CPT codes relevant to this patient group (15756 free muscle or myocutaneous flap with microvascular anastomosis, 15757 free skin flap with microvascular anastomosis, 15736 pedicled muscle, myocutaneous or fasciocutaneous

flap upper extremity, 15738 pedicled muscle, myocutaneous or fasciocutaneous flap lower extremity and 15734 pedicled muscle, myocutaneous or fasciocutaneous flap trunk) and patients were categorized accordingly. Patient body mass index was categorized into five groups; underweight (BMI < 18.5), normal (18.5 < BMI ≤ 25), overweight (25 < BMI ≤ 30), obese 1 (30 < BMI ≤ 35), obese 2 (35 < BMI ≤ 40) and obese 3 (BMI > 40).



Data were entered in the calculator for each patient and the predicted complications were recorded. The actual rate of 30-day post-operative complications was then determined from our institutional prospective sarcoma database and patient chart review. The observed complications were categorized into the options provided by the calculator. *Any complication* included superficial incisional surgical site infection, deep incisional surgical site infection, organ space surgical site infection, wound disruption, unplanned intubation, pulmonary embolism, deep vein thrombosis, ventilator > 48 hr, progressive renal insufficiency, acute renal failure, urinary tract infection, stroke, cardiac arrest, myocardial infarction, return to the operating room or systemic sepsis and *serious complication* included cardiac arrest, myocardial infarction, pneumonia, progressive renal insufficiency, acute renal failure, pulmonary embolism, deep vein thrombosis, return to the operative room, deep incisional surgical site infection, organ space surgical site infection, systemic sepsis, unplanned intubation, urinary tract infection and wound disruption. The predicted risk was compared to the observed rate of complications to determine the accuracy of the calculator as a predictive tool in this patient population.

Statistical Analysis

Statistical analysis was performed using R version 3.0.2. p-values less than or equal to 0.05 were considered significant. Mean, standard deviation and range of all continuous variables and frequency of all categorical variables were calculated. Bivariate analysis was performed to compare the overall rate of the predicted risk of complications with the observed risk of complications. The accuracy of the model was assessed for both calibration and discrimination using the same statistical tools that were used in the original validation of the calculator. Calibration measures how well the predicted risk of complication matches the observed complication rate and was assessed using the Hosmer-Lemeshow (H-L) goodness of fit test.

Discrimination measures how well the model can separate those who are at risk of complications from those who are not and was measured using c-statistics or the area under the Receiver Operating Characteristics (ROC) curve. The ideal model of

discrimination would have a value approaching 1 while a value close to 0.5 indicates that the model has a random performance. Brier's score, defined as the average squared difference between patients' predicted probabilities and observed outcome, was also determined as this is a more global measurement that simultaneously combines both calibration and discrimination and was favored by the developers of the ACS NSQIP risk calculator in the validation of their model. In a perfect model of prediction the Brier's score will approach 0.

Results

Two hundred and sixty-five patients underwent flap reconstruction following STS resection. The mean age was 59.1 ± 18.5 years and mean BMI was 26.8 ± 6.7. Patient demographics and risk factors recorded in the calculator are outlined in Table 1. Bivariate analysis did not identify an association between any of the variables recorded in the calculator and increased complication rates ($p>0.05$ in all cases, Table 1).

TABLE 1

Patient demographics and risk factors as recorded in the risk calculator and bivariate analysis for complications

			Complications		
Variable / risk Factor		**N=265 (%)**	**No**	**Yes**	**p-value**
Sex	Male	149 (56%)	101	48	
	Female	116 (44%)	78	38	0.93
Functionally independent	No	6 (2%)	5	2	0.89
	Yes	259 (98%)	174	84	
Emergency	No	265 (100%)			N/A
	Yes	0 (0%)			
ASA class	1	16 (6%)	14	2	0.29
	2	98 (37%)	67	31	
	3	134 (51%)	86	48	
	4	17 (6%)	12	5	
Wound class clean	No	4 (1%)			N/A
	Yes	263 (99%)			
Chronic steroid use	No	265 (99%)			N/A
	Yes	2 (1%)			
Ascites	No	265 (100%)			N/A
	Yes	0 (0%)			
Systemic sepsis	No	265 (100%)			N/A
	Yes	0 (0%)			
Ventilator dependent	No	265 (100%)			N/A
	Yes	0 (0%)			

- Table 1 continued -

Disseminated cancer	No	247 (93%)	169	78	0.26
	Yes	18 (7%)	10	8	
Diabetes	No	240 (90%)	166	74	0.08
	Oral	18 (7%)	13	12	
	Insulin	7 (3%)			
Dialysis	No	265 (100%)			N/A
	Yes	0 (0%)			
Dyspnea	No	247 (93%)	170	77	0.1
	Yes	18 (7%)	9	9	
Hypertension	No	170 (64%)	119	51	0.25
	Yes	95 (36%)	60	35	
Previous cardiac event	No	243 (92%)	161	82	0.24
	Yes	22 (8%)	18	4	
Congestive heart failure	No	262 (99%)			N/A
	Yes	3 (1%)			
Severe COPD	No	256 (97%)	173	83	0.62
	Yes	9 (3%)	6	3	
Acute renal failure	No	265 (100%)			N/A
	Yes	0 (0%)			
Current smoker	No	214 (81%)	147	67	0.42
	Yes	51 (19%)	32	19	
BMI	Underweight	14 (5%)	11	3	0.16
	Normal	98 (37%)	72	26	
	Overweight	89 (34%)	53	36	
	Obese 1	34 (13%)	26	8	
	Obese 2	20 (7%)	11	9	
	Obese 3	10 (4%)	6	4	
Age	< 65 years	157 (59%)	112	45	0.17
	65-74 years	46 (17%)	31	15	
	75-84 years	49 (18%)	28	21	
	≥ 85 years	13 (5%)	8	5	

BMI: body mass index; N/A: not applicable; statistical comparisons were not performed for variables occurring in ≤ 1% of the study population.

Tumours were resected from the lower extremity (52%), upper extremity (33%) and trunk (15%). Pedicled flaps were performed in 186 patients while 79 had free flaps (Table 2).

The actual observed rates of complications in our patient cohort were 32.5% and 15.9% for *any complication* and *serious complications* respectively. The observed complications are outlined in Table 3. Forty-two patients experienced serious complications as defined by the calculator, the majority (n = 36) of which were returns to the operating room for secondary surgery. The most common indication for a return to the operating room was a wound infection. Flap related complications required secondary surgery in 15 patients with total flap loss occurring in six (2.3%). Other serious complications included

TABLE 2

Distribution of pedicled and free Flaps

Flaps	n	(% of total)
Pedicled flaps (n=186)		
Gastrocnemius	58	(22%)
Latissimus dorsi	44	(17%)
Radial forearm	27	(10%)
Anterolateral thigh	17	(7%)
Rectus abdominus	17	(7%)
Perforator	6	(2%)
Gluteus maximus	5	(1.8%)
Soleus	3	(1%)
Tensor fascia lata	2	(0.8%)
Pectoralis	2	(0.8%)
Paraspinal	1	(0.3%)
Gracilis	1	(0.3%)
Rectus femoris	1	(0.3%)
Semimembranosus	1	(0.3%)
Trapezius	1	(0.3%)
Free flaps (n=79)		
Anterolateral thigh	46	(17%)
Latissimus dorsi	16	(6%)
Rectus abdominus	8	(3%)
Radial forearm	6	(2%)
Gracilis	2	(0.8%)
Parascapular	1	(0.3%)

myocardial infarction (n = 2), deep vein thrombosis (n = 2), pulmonary embolism (n = 1) and systemic sepsis (n = 1).

The mean predicted rate of *any complication* was 15.35 ± 5.6% while the mean predicted rate for *serious complications* was 10.7 ± 3.9%. This differed significantly from the actual observed complication rates (32.5%, p=0.009 and 15.9, p=0.041 for *any* and *serious complications* respectively). The predicted risk of the most commonly recorded complication (return to operating room) was 7.7%, which was significantly lower than the rate observed in our cohort (13.6% p=0.038)

TABLE 3

Observed complications in the study group

Complication	n	% (of total)
Minor complications	**44**	**16.6**
Infection	21	7.9
Dehiscence	10	3.8
Delayed wound healing	8	3.0
Partial necrosis	4	1.5
Urinary tract infection	1	0.4
Serious complications	**42**	**15.9**
Return to operation room	36	13.6
Infection	13	4.9
Hematoma	5	1.9
Dehiscence	3	1.1
Flap compromise	4	1.5
Partial flap loss	5	1.9
Total flap loss	6	2.3
Myocardial infarction	2	0.8
Deep vein thrombosis	2	0.8
Systemic sepsis	1	0.4
Pulmonary embolism	1	0.4
Total	**86**	**32.5**

Minor complications are those recorded as "any complication" that did not reach the criteria for "serious complication" as defined by the calculator. Complications were classified as minor if they did not require readmission or return to the operating room for secondary surgical procedures

The risk calculator model exhibited a lack of fit based on the H-L test of calibration ($p \leq 0.001$ for any complication) indicating that the predicted number of complications did not match the actual number of complications in this patient population.

Based on receiver operating curve (ROC) analysis the area under the curve (AUC) for any complication was found to be 0.626 (Figure 1). An ideal model of discrimination would have an AUC of 1.0 while a value closer to 0.5 indicates random performance of the tool.

The Brier's Score for any complication was 0.242, which was significantly different from 0 ($p<0.001$). This indicates a poor correlation between the observed and predicted probability of complications and is illustrated in Figure 2.

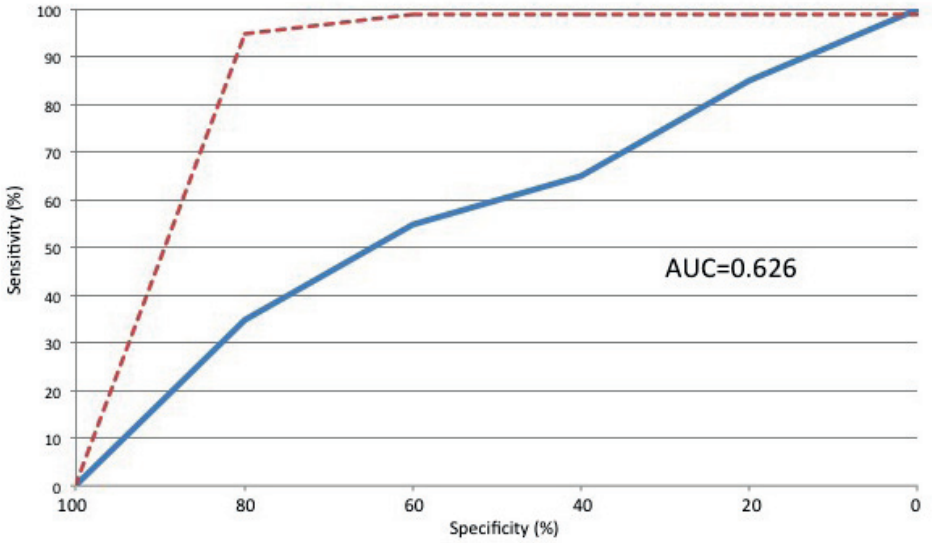


Figure 1. Area under the receiver operating curve (ROC; c-statistic) indicating poor discriminatory power of the model for any complication (solid blue line). Dashed red line shows ideal model where area under the curve would be greater than 0.8.

Discussion

This study demonstrates that the ACS-NSQIP surgical risk calculator is not the ideal tool for identifying STS patients at risk for complications following flap reconstruction. The calculator significantly underestimated the overall rate of complications in this patient cohort. The low c-statistic value of 0.626 confirmed that the calculator had poor discriminatory value in this population and was unable to effectively differentiate between patients who would develop complications post-operatively and those who would not. This contrasts with the higher c-statistics (>0.8) reported by the developers in their validation of the model. In addition the high Brier's score of 0.242 indicates that the calculator had low predictive power in this series.

This universal risk calculator was developed from a disease specific colorectal risk calculator and was subsequently validated in a similar patient population.[17] The results of our study are perhaps unsurprising as it is ambitious to expect a single tool to be able to accurately predict complications for a diverse range of surgical procedures. Our findings support previous reports demonstrating lack of validity of the universal risk calculator in both arthroplasty and pulmonary surgery.[20,21] Many of the parameters collected in the calculator pertain to acutely ill patients and may be less relevant to elective surgery. Although the patient cohort in this study was a heterogenous group

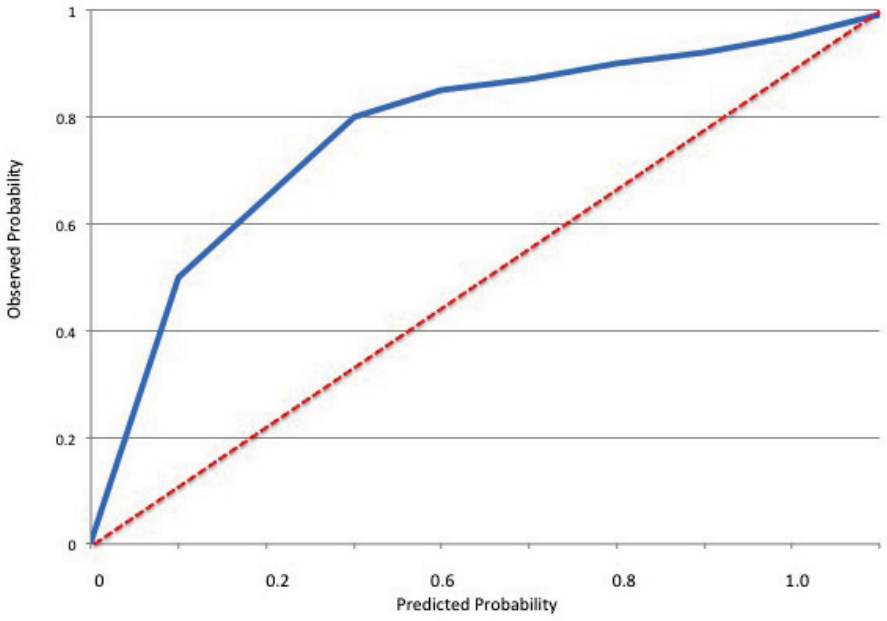


Figure 2. Relationship between the predicted and observed probability of any complication (solid blue line). Dashed red line indicates the linear relationship between predicted and observed risk in an ideal model of prediction. Brier's score 0.242 ($p<0.001$).

with a wide age range and a relatively high rate of comorbidities they were unlikely to have severe disease such as acute renal failure, systemic sepsis or ventilator dependence. Nine of the 21 parameters included in the calculator were recorded in less than 1% of the patients in our study. Conversely, other factors that we know to be clinically relevant in the assessment of risk in the context of sarcoma resection and flap reconstruction are not considered.[22-24] Conditions such as peripheral vascular disease, connective tissue disease, autoimmune disease or clotting disorders are not included in the risk assessment. The size and site of the tumour can be expected to have significant impact on the complication rate following surgery.[25,26] Adjuvant therapies such as chemotherapy and most importantly pre-operative radiation are known to have a major impact on wound healing complication rates both with and without flap reconstruction following resection of STS but are not recorded in this model.[27-29]

The calculator cannot accommodate multiple procedure codes, which limits its usefulness in complex multidisciplinary cases. In this study flap procedure codes were used in all cases but the complications recorded resulted from a combination of both extirpative and reconstructive procedures. The discrepancy between predicted and

observed complications rates may be due to the omission of factors related to the tumour itself and its resection. The complexity of the tumour based on the involvement of deep structures, as well as the need for vascular, neural or bony reconstruction vary greatly between patients. The calculator includes multiple CPT codes for radical tumour resection and it is possible that these may give more precise risk predictions, but they were not assessed in this study. The CPT codes provided for soft tissue reconstruction may also be a source of discrepancy. Free flap codes do not consider the site of reconstruction as they are categorized according to the constituents of the flap (myocutaneous or fasciocutaneous) while pedicled flaps are divided by anatomical site (trunk, upper limb or lower limb) and so do not consider the type of flap used.

We acknowledge that our study has limitations. The calculator was developed using cumulative data from multiple centres while our validation uses data collected at a single high volume institution. Previous studies have cautioned against the extrapolation of the NSQIP dataset to institutional complication rates in the context of elective and reconstructive surgery. Although most of the clinical data was obtained form our prospective database information regarding some complications and comorbidities were collected retrospectively which may have lead to some inaccuracies. Observed complications were adjusted to fit the categories of the calculator, which may introduce an element of subjectivity. The developers acknowledge that the risk calculator cannot incorporate all relevant parameters for every individual procedure codes. The calculator therefore includes a function that allows surgeons to adjust the risk if they feel there was a salient factor that was not recorded. This, however, adds a subjective element and reduces the value of the calculator as an objective tool and was not used in this study. This “Surgeon Assessment Score” was not formally modeled in the development of the calculator and there is no quantitative evidence that this adjusted risk is more accurate. Our study only examined risk factors included in the calculator itself and while it demonstrates that these factors do not correlate with complication rates we did not examine other factors that may predict complications and as such this study does not provide the basis for the development of an alternative risk assessment tool.

Although the universal risk calculator is a very attractive concept, a disease specific calculator may prove more effective in the prediction of risk in this population as it could incorporate more pertinent patient, surgery and disease specific data related to elective STS resection and flap reconstruction. Recognition of the importance of tumour size, neo-adjuvant radiation and complexity of surgery and the ability to combine procedure codes in cases of complex reconstruction may enhance the accuracy of the tool. In addition, the NSQIP calculator only considers complications that occur

in the first 30 days post-operatively. In this patient group information on longer term sequelae such as need for reoperation, locoregional recurrence and functional outcome may be of significant assistance to patients in their decision making process.

Conclusion

The ACS NSQIP surgical risk calculator does not accurately predict complications in patients undergoing reconstruction following wide surgical resection of STS. This study highlights the importance of validation of this universal tool in individual patient populations and perhaps the need for disease specific calculators to provide individualized pre-operative risk assessment.

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CHAPTER 4

Patient, tumour and treatment factors affect complication rates in soft tissue sarcoma flap reconstruction in a synergistic manner

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Abstract

Introduction: Flap reconstruction plays an essential role in the management of soft tissue sarcoma, facilitating wide resection while maximizing preservation of function. The addition of reconstruction increases the complexity of the surgery and identification of patients who are at high risk for post-operative complications is an important part of the pre-operative assessment. This study examines predictors of complications in these patients.

Methods: 294 patients undergoing flap reconstruction following sarcoma resection were evaluated. Data on patient, tumour and treatment variables as well as post-operative complications were collected. Bivariate and multivariate regression analysis was performed to identify independent predictors of complications. Analysis of synergistic interaction between key patient and tumour risk factors was subsequently performed.

Results: A history of cerebrovascular events or cardiac disease were found to be the strongest independent predictors of post-operative complications (OR 14.84, p=0.003 and OR 5.71, p=0.001 respectively). Further strong independent tumour and treatment-related predictors were high grade tumours (OR 1.91, p=0.038) and the need for additional reconstructive procedures (OR 2.78, p=0.001). Obesity had significant synergistic interaction with tumour resection diameter (RERI 1.1, SI 1.99, p=0.02) and high tumour grade (RERI 0.86, SI 1.5, p=0.01). Comorbidities showed significant synergistic interaction with large tumour resections (RERI 0.91, SI 1.83, p=0.02).

Conclusion: Patient, tumour and treatment–related variables contribute to complications following flap reconstruction of sarcoma defects. This study highlights the importance of considering the combined effect of multiple risk factors when evaluating and counselling patients as significant synergistic interaction between variables can further increase the risk of complications.

Key Words: Soft tissue sarcoma, flap reconstruction, complications

Introduction

Wide surgical resection is the cornerstone of management for most patients with soft tissue sarcoma (STS) and in many cases this would not be possible without the addition of soft tissue reconstruction.[1,2] Plastic surgery plays a key role in the multidisciplinary management of sarcoma patients as advances in reconstructive techniques facilitate the ability to perform extensive resections while still providing coverage for vital structures and prostheses.[3-5] This combined approach enables effective oncological ablation while maximizing preservation of function.[4,6,7]

Although the benefits of soft tissue reconstruction are clear, the addition of free or pedicled flaps increases the complexity of the surgery, which extends both the operative and recovery times.[4,8,9] Identifying patients who are at high risk for post-operative complications is important in the pre-operative assessment. Even in cases where the surgical strategy will not change, accurate and personalized estimation of risk is a critical component of effective pre-operative counselling to ensure that patients understand the risks and benefits of the proposed treatment and so that any reversible or modifiable medical conditions can be addressed.[10-13]

The complications of complex soft tissue reconstruction in the context of sarcoma ablation are poorly characterized in the current literature. Similarly the factors that may predispose to such complications are infrequently investigated in this patient population.[9,14,15] The primary objective of this study was to identify independent predictors of post-operative complications in patients undergoing flap reconstruction following wide resection of soft tissue sarcoma. We specifically examine the significance of patient, treatment and tumour factors and determine if there is a synergistic interaction between these variables in patients with multiple risk factors.

Methods

Institutional research ethics board approval was obtained for this study. Patients who underwent resection of a soft tissue sarcoma from the extremities or trunk and required soft tissue reconstruction with a pedicled or free flap between January 2006 and January 2015 were identified from a prospectively maintained database at Mount Sinai Hospital, Toronto, Canada.

Patient demographics (age, sex, body mass index [BMI] and smoking status),

comorbidities and medications, tumour variables (histology, location, tumour depth, stage, grade and diameter of resected tissue; this includes the tumour together with the surrounding soft tissue), adjuvant therapies (radiation, chemotherapy) and operative details (primary or secondary excision, tissues resected, timing of reconstruction, flap details, additional reconstructive procedures and duration of surgery) were collected from the database and retrospective chart review. All post-operative surgical and medical complications were recorded and graded according to the Clavien-Dindo classification of surgical complications.[16]

Statistical analysis

Statistical analyses were performed using SAS v9.4 (SAS institute; Cary, NC). The mean, standard deviation and range of all continuous variables and frequency of all categorical variables were calculated. Bivariate analysis was performed to determine the association between variables and post-operative complications. Wilcoxon rank sum test was used for continuous variables and Chi-square test and Fisher's exact test were used for categorical variables to determine the significance of the association, with p-values <0.05 considered significant. Multivariate logistic regression models were then constructed to identify independent predictors of post-operative complications. The accuracy of the model was confirmed using the Hosmer-Lemeshow goodness of fit test and c-statistics.[17]

To determine whether there were interactions between significant predictors of complications, three measures of interaction were calculated. The relative excess risk due to interaction (RERI) measures the extent to which risk increases in the presence of two risk factors compared to the sum of the individual risks. The attributable proportion (AP) standardizes the RERI as a proportion of risk due to the interaction of two risk factors and the synergy index (SI) is the ratio of the risk of the joint effect to the sum of the individual risks. A RERI or AP > 0 and SI > 1 indicates positive synergistic interaction between risk factors.[18]

Results

A total of 294 patients underwent STS resection followed by flap reconstruction and were evaluated in this study. The study group included 164 males and 130 females with a mean age of 58.9 years (± 18.9, range 18-97) and mean BMI of 26.9 (± 6.6, range 15-63.8). Almost half the study population (48%) had at least one comorbidity. Patient demographics and comorbidities are outlined in detail in Table 1.

TABLE 1

Patient, tumour and treatment details and bivariate analyses for complications

				Complication		
		n=294	%	No n=181 (62%)	Yes n=113 (38%)	p-value
Patient characteristics						
Age (years)	Mean ± SD	58.9	± 18.3	57.3 (±17.9)	61.4 (±18.7)	**0.02**
	≥65	116	39.5	63	53	
	< 65	178	60.5	118	60	**0.04**
BMI (kg/m^2)	Mean ± SD	26.9	± 6.6	26.3 (±6.8)	27.9 (±6.3)	**0.006**
	≥30	65	22.1	36	29	
	<30	229	77.9	145	84	0.25
Sex	Female	130	44.2	80	50	
	Male	164	55.8	101	63	0.99
Pre-op Heamoglobin	Low	101	34.4	49	52	
	Normal	183	62.2	125	58	**0.001**[a]
ASA class	1 or 2	130	44.2	86	44	
	3 or 4	164	55.8	95	69	0.15
Active smoking <30 days	No	241	82	151	90	
	Yes	53	18	30	23	0.41
Anticoagulants	No	239	81.3	155	84	
	Yes	55	18.7	26	29	**0.02**
Pain medication	No	226	76.9	143	83	
	Yes	68	23.1	38	30	0.27
Immunosuppressive	No	285	96.9	174	111	
medication	Yes	9	3.1	7	7	0.49
Any comorbidity	No	153	52	106	47	
	Yes	141	48	75	66	**0.005**
Diabetes	No	258	87.8	164	94	
	Yes	36	12.2	17	19	0.059
Hypertension	No	186	63.3	124	62	
	Yes	108	36.7	57	51	**0.02**
Cardiovascular disease	No	249	84.7	163	86	
	Yes	45	15.3	18	27	**0.001**
Cerebrovascular disease	No	280	95.2	178	102	
	Yes	14	4.8	3	11	**0.003**
Congestive heart failure	No	286	97.3	179	107	
< 30 days	Yes	8	2.7	2	6	0.058
COPD history	No	284	96.6	176	108	
	Yes	10	3.4	5	5	0.51
Thyroid disease	No	272	92.5	170	102	
	Yes	22	7.5	11	11	0.25
Vascular disease	No	288	97.9	178	110	
	Yes	6	2.1	3	3	0.68
Other comorbidities	No	281	95.5	177	104	
	Yes	13	4.5	4	9	**0.04**
Tumour / treatment details						
Total duration operation (hours)	Mean ± SD	6,69	±3.32	6.31 (±3.17)	7.30 (±3.48)	**0.014**
Total days in hospital	Mean ± SD	11.8	±9.2	10.1 (±7)	14.4 (±11.5)	**<0.001**
Diameter of resection	≥10 cm	220	74.8	129	91	
	<10 cm	64	21.8	47	17	**0.032**[b]

- Table 1 continued -

				Complication		
		n=294	**%**	**No n=181 (62%)**	**Yes n=113 (38%)**	**p-value**
Presenting status	Local recurrence	24	8.1	13	11	
	Primary tumour	270	91.8	168	102	0.44
Prior surgery	No	211	71.8	127	84	
	Yes	83	28.2	54	29	0.44
Tumour site	Lower limb	181	61.6	103	78	
	Upper limb	85	28.9	58	27	
	Trunk	28	9.5	20	8	0.11
Tumour depth	Deep	193	65.7	114	79	
	Superficial	101	34.3	67	34	0.22
Tumour grade	1/2	110	37.4	80	30	
	3	180	61.2	100	80	**0.003**[c]
Tumour stage	1/2	171	58.2	116	55	
	3/4	120	40.8	62	58	**0.005**[c]
Surgical resection margin	Positive	45	15.3	29	16	
	Negative	248	84.4	151	97	0.65[c]
Residual	No prior surgery	216	73.5	131	85	
	No	21	7.1	12	9	
	Yes	56	19.1	38	18	0.55[d]
Pre-operative radiotherapy	No	77	26.2	50	27	
	Yes	217	73.8	131	86	0.48
Pre-operative chemotherapy	No	276	93.9	167	109	
	Yes	18	6.1	14	4	0.21
Immediate reconstruction	No	12	4	6	6	
	Yes	282	96	175	107	0.40
Flap characteristics	Fasciocutaneous	103	35	69	34	
	Muscle	191	65	112	79	0.16
	Free flap	79	26.9	45	34	
	Pedicled flap	215	73.1	136	79	0.33
Total number of tissue removed	0-2	198	67.3	129	69	
(skin, muscle/tendon, bone, nerve, vessel)	3-5	90	30.6	50	40	0.12[e]
Additional reconstructive procedures	No	179	60.9	120	59	
	Yes	115	39.1	61	54	**0.02**
Vascular repair	No	284	60.9	177	107	
	Yes	10	39.1	4	6	0.19
Bone/joint repair	No	276	96.6	174	102	
	Yes	18	3.4	7	11	**0.04**
Tendon/joint repair	No	213	93.9	135	78	
	Yes	81	6.1	46	35	0.30
Abdominal repair	No	280	72.5	174	106	
	Yes	14	27.5	7	7	0.36

BMI = body mass index

a. Excluding missing values of 10 patients

b. Excluding patients undergoing delayed reconstruction

c. Excluding cases where stage/grade/margin could not be determined

d. Excluding cases that did not have prior surgeries

e. Excluding patients undergoing delayed reconstruction

The majority of tumours were located in the lower limbs (62%), with the remainder in the upper limbs (29%) and trunk (9%). Two thirds of tumours were categorized as deep (66%) indicating that they were deep to or involved the deep fascia. A large tumour resection was considered as a tumour resection diameter ≥10 cm, which was present in 75% of cases. Neoadjuvant radiotherapy was administered in most cases (74%) to a total dose of 50 Gy given in 25 daily fractions of 2 Gy over 5 weeks, with surgical resection planned 4-6 weeks after the completion of pre-operative radiation. Conversely relatively few patients (6%) had pre-operative chemotherapy. The vast majority of soft tissue reconstructions (96%) were performed immediately after tumour resection as part of the same operation. Tumour and treatment details are outlined in Table 1. Two hundred and fifteen patients (73%) had pedicled flaps while free flaps were performed in 79 cases (27%). The flaps performed in the study group are described in Table 2.

One hundred and thirteen patients (38%) developed a post-operative complication in this series. Of these, 11 patients experienced more than one complication. The majority of the complications included minor issues which were treated conservatively, such as a wound infection, dehiscence or delayed wound healing (Clavien-Dindo grade ≤2; 22.5%), and 20 percent were major complications (Clavien-Dindo grade ≥2). Forty-five patients (15% of cases) required a return to the operating room for secondary surgical intervention. Total or partial flap loss occurred in 2.4% (n=7) and 2.7% (n=8) of patients respectively. Medical complications were relatively rare, occurring in 8.5% of cases. Details of the complications are listed in Table 3. Patients who developed any complication had significantly longer operative procedures ($p=0.01$) and hospital length of stay ($p<0.001$).

A variety of patient factors were found to be associated with complications including age ≥65 years, high BMI, low pre-operative haemoglobin, use of anticoagulants and comorbidities (Table 1). Similarly tumour and treatment factors including diameter of resection, need for additional reconstructive procedures (including bone, nerve, tendon and/or major blood vessel repair) as well as high tumour grade (defined as grade 3) and stage (defined as stage 3/4) were found to be significantly associated with the risk of developing complications (Table 1). Neither pre-operative radiation nor chemotherapy were found to be associated with complication rates in this series. The location of the tumour and the type of flap used for reconstruction did not influence the development of complications.

TABLE 2

Overview of pedicled and free flaps performed

	n	(% of total)
Pedicled flaps (n=215, 73%)		
Gastrocnemius	62	(21)
Latissimus dorsi	43	(15)
Radial forearm	26	(9)
Sartorius	23	(8)
Rectus abdominus	17	(6)
Anterolateral thigh	16	(5)
Perforator	7	(2)
Gluteus maximus	5	(1.8)
Soleus	3	(1)
Pectoralis	3	(1)
Gracilis	3	(1)
Tensor fascia lata	2	(0.7)
Vastus lateralis	1	(0.3)
Rectus femoris	1	(0.3)
Semimembranosus	1	(0.3)
Paraspinal	1	(0.3)
Trapezius	1	(0.3)
Free flaps (n=79, 27%)		
Anterolateral thigh	46	(16)
Latissimus dorsi	16	(5)
Rectus abdominus	8	(3)
Radial forearm	6	(2)
Gracilis	2	(0.7)
Parascapular	1	(0.3)

Variables identified as being significant in univariate analysis were selected for inclusion in the multivariate assessment model (Table 4). A history of cerebrovascular events (defined as stroke or transient ischaemic attacks) or cardiac disease (defined as myocardial infarction, coronary artery disease, valvular disease or arrhythmias) were found to be the strongest independent predictors of post-operative complications (OR 14.84, p=0.003 and OR 5.71, p=0.001 respectively). Overall complication rates were high in patients with cardiovascular or cerebrovascular histories (60% and 79% respectively compared to 38% in the study group in general, p=0.012 and p=0.008 respectively).

TABLE 3

Post-operative complications in the study group

Complications classified according to the Clavien-Dindo system*	**n**	**%**
Grade 1	**16**	**5.4**
Dehiscence	7	2.4
Delayed wound healing	7	2.4
Infection	1	0.3
Hematoma	1	0.3
Grade 2	**50**	**17.0**
Wound related	*28*	*9.5*
Infection needing abs p.o.	9	3.1
Infection needing abs i.v.	9	3.1
Dehiscence	6	2.0
Delayed wound healing	3	1.0
Partial necrosis	1	0.3
Medical	*22*	*7.5*
Delirium	7	2.4
Arrhythmia	4	1.4
≥ 3 Transfusions	3	1.0
Deep vein thrombosis	3	1.0
Pneumonia	2	0.7
Urinary tract infection	1	0.3
Endocarditis	1	0.3
Pulmonary embolism	1	0.3
Grade 3	**56**	**19.0**
Grade 3a	*11*	*3.7*
Infection	3	1.0
Seroma	2	0.7
Delayed wound healing	1	0.3
Partial necrosis	5	1.7
Grade 3b	*45*	*15.3*
Infection	13	4.4
Dehiscence	6	2.0
Hematoma	3	1.0
Delayed wound healing	4	1.4
Flap compromise	4	1.4
Partial flap loss	8	2.7
Total flap loss	7	2.4
Grade 4	**2**	**0.7**
Myocardial infarction	1	0.3
Systemic sepsis	1	0.3
Total complications	**124**	**42.2**
Total patients developing a complication[a]	**113**	**38.4**

* Clavien-Dindo classification: Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I. Grade III: Requiring surgical, endoscopic or radiological intervention (a: under local anesthesia; b: under general anesthesia). Grade IV: Life-threatening complication requiring IC/ICU (a: single organ; b: multiorgan dysfunction). Grade V: Death.
[a] 11 patients experienced >1 complication, and each was counted as one complication event in the statistical analyses.

TABLE 4

Multivariate assessment of independent risk factors for complications

Characteristic	OR	95% CI		p-value
Age ≥65 years	1.00	0.98	1.01	0.63
Body mass index ≥30 kg/m^2	1.06	1.01	1.11	**0.012**
Having a comorbidity	1.32	0.65	2.68	0.44
Cardiovascular disease	5.71	2.01	16.22	**0.001**
Cerebrovascular disease	14.84	2.46	89.67	**0.003**
Use of anticoagulants	0.44	0.17	1.19	0.11
Low pre-operative haemoglobin	1.95	1.00	3.80	0.052
Diameter of resection ≥10cm	1.04	1.00	1.09	**0.035**
High tumour grade	1.91	1.04	3.51	**0.038**
Additional reconstructive procedures	2.78	1.54	5.03	**0.001**
Hosmer-Lemmeshow p-value	0.86			
C statistic	0.77			

As might be expected the majority of major medical complications occurred in these groups (36% and 16% respectively). Major wound complication rates were also increased in patients with cardiovascular disease (25% compared to 15% in the study group in general, p=0.032). The tumour factors high grade and large tumour resection as well as the treatment factor need for additional reconstructive procedures were also found to be important independent predictors of complications (OR 1.91, p=0.038, OR 1.04, p=0.035 and OR 2.78, p=0.001 respectively).

We then examined whether important patient-related (BMI ≥30 and comorbidities), tumour-related (large resection diameter, high tumour grade) and treatment-related (need for additional reconstructive procedures) risk factors might have a synergistic interaction and increase the chance of developing complications. In the presence of obesity the risk of developing complications increased for all 3 tumour risk factors. Patients with large tumour resections had a greater risk of developing complications if they also had comorbidities (Table 5). We then determined the extent to which these findings were due to interaction rather than simply a sum of the individual risks (Table 5). This confirmed that obesity had significant interaction with large tumour resections (RERI 1.1, SI 1.99, p=0.02) and high tumour grade (RERI 0.86, SI 1.52, p=0.01). Comorbidities showed significant synergistic interaction with large tumour resections (RERI 0.91, SI 1.83, p=0.02).

TABLE 5

Adjusted odds ratios for the joint effects of tumour, patient and treatment-related factors and measures of their synergistic interaction

	Tumour and treatment factors														
	Diameter of resection ≥10cm					**High tumour grade**					**Additional reconstructive procedures**				
	OR	p-value	RERI	AP	SI	OR	p-value	RERI	AP	SI	OR	p-value	RERI	AP	SI
Obesity alone	1.35	0.70				1.71	0.33				2.15	0.09			
Tumour factor alone	1.76	0.19				1.95	0.06				3.00	<0.01			
Obesity + tumour/treatment factor	3.22	**0.02***	1.10	0.34	1.99	3.52	**0.01***	0.86	0.24	1.52	4.01	0.01	-0.14	-0.04	0.95
Comorbidities alone	1.06	0.94				1.96	0.24				1.85	0.19			
Tumour factor alone	1.68	0.32				2.47	0.04				3.80	<0.01			
Comorbidities + tumour/treatment factor	3.18	**0.02***	0.91	0.34	1.83	2.78	0.03	-0.65	-0.23	0.73	3.61	0.01	-1.04	-0.29	0.72

RERI=relative excess risk due to interaction; AP=attributable proportion due to interaction; SI=synergy index.

* Denotes statistical significant positive synergistic interaction ($p<0.05$)

Discussion

This study examined predictors of post-operative complications in patients undergoing reconstruction of soft tissue sarcoma defects in a large series at a tertiary cancer centre. Patient, tumour and treatment related variables were all found to contribute to increased risk of complications. In addition tumour and patient variables showed evidence of synergistic interaction further increasing the risk of complications in the presence of more than one risk factor.

We identified a number of variables that can significantly impact the development of both medical and surgical post-operative complications in patients with STS undergoing flap reconstruction. Significant patient variables included obesity and prior history of cerebrovascular or cardiovascular disease while the tumour related variable of resection diameter and high grade and the treatment variable need for additional reconstructive procedures were also found to be important. While a high BMI may not be modifiable in the acute cancer setting, patients with cerebrovascular or cardiovascular disease may be amenable to risk assessment and intervention prior to surgical management. Identification of specific risk factors is essential to pre-operative patient counselling since beyond possible risk modification, the provision of accurate information on the risks and benefits of treatment has been identified as a key target in improving the quality of cancer care.[19]

As might be anticipated increased diameter of resected tissue was found to be a significant predictor of post-operative complications as larger soft tissue defects would be more challenging to cover and lead to higher rates of wound complications such that total or partial flap failure might be expected.[20-23] While composite resections of multiple tissues did not influence the development of complications, the need for reconstruction of deep structures was found to be a significant risk factor. Previous studies have identified an association between vascular reconstruction and complications[24-26] but in this study only osseous reconstruction was individually associated with complications ($p=0.04$). This may reflect the increased complexity of cases that required use of tumour prostheses or bone allografts and the associated risk of infection with use of alloplastic materials.

Although pre-operative radiation is considered a risk factor for post-operative complications, we did not find this to be the case in this series. Previous studies have reported higher wound complication rates in sarcoma patients who have received radiation but in many cases the wounds were closed primarily and their findings may not

apply to flap reconstructions.[20,21,27] As pedicled and free flaps import well-vascularized tissue that has not been exposed to radiation it is possible that they mitigate the effects of radiation on wound healing. Pre-operative radiation is the standard protocol at our centre and we therefore have significant experience performing complex reconstructions in recently radiated fields and our flap success rate is unaffected by prior radiation.[28] Accordingly, we may have a lower threshold for performing flap reconstruction compared to other institutions where patients have not received pre-operative radiation. We acknowledge that our findings may not be applicable to other centres. Tumour location has also been reported to influence the development of complications but this study found no significant difference between complication rates in tumours of the upper or lower limbs.[29-31] Similarly others have shown increased wound problems when tumours are located close to the skin[32,33] but this was not the case in our study where deep rather than superficial lesions were found to be more predictive of post-operative complications.

Flap coverage facilitates tension free closure that does not rely on compromised native skin flaps for healing. These benefits may help mitigate the effects of risk factors that have been identified as significant for complications in cases where flaps are not used.

The findings of this study support the theory that immediate reconstruction may have favourable effects on post-operative wound healing and also suggest that the effects of risk factors on complications differ when flap reconstruction is included in surgical management.[2,20,21] This highlights the importance of considering risk factors specific to STS patients undergoing flap reconstruction as they may differ considerably from risk factors in patients undergoing primary wound closure, which have been extensively studied. Similarly patients with STS differ from patients having flap reconstructions for defects at other anatomic sites such as the head and neck, breast or extremities secondary to trauma, where other predictors of complications have been identified.

Recognition of possible interactions between risk factors aids the development of a more comprehensive individualized risk profile. Our study demonstrated significant synergistic interactions suggesting that patient variables can further increase the impact of tumour related risk factors. Synergy indicates that the effect of two risk factors in combination exceeds the sum of their individual effects. The combination of obesity and large tumours doubled the effect of these individual risk factors (SI 1.99). Similarly when obesity and high tumour grade occurred simultaneously the effect on complications was increased by a factor of 1.5 (SI 1.52). While comorbidities in general did not increase the risk of complications in our series we noted that when combined with large tumour

resection diameter, the combination significantly increased complication rates and the synergistic effect of these variables was almost double the sum of the individual risks (SI 1.83). Although it might be expected that larger and more complex tumours would have higher complication rates in older patients, this was not found to be the case. This result show that the development of complications is multifactorial and that pre-operative assessment must consider risk factors in the context of the presence or absence of other variables.

We previously reported that the American College of Surgeons NSQIP Surgical risk calculator failed to identify patients at risk of complications following flap reconstruction of STS defects.[34] We hypothesized that failure to consider tumour-specific factors may have compromised the efficacy of the tool and this is supported by the results of the current study which confirmed that tumour related variables are important predictors of complications and can increase the significance of patient related variables such as obesity and comorbidity that are included in the calculator.

This is, to our knowledge, the most comprehensive study of factors contributing to complications following flap reconstruction of STS defects. We have identified significant patient, treatment and tumour-related risk factors that are specific to this patient population. Accurate risk prediction remains a significant challenge, particularly in complex and diverse procedures such as STS reconstruction. This study is an important step in delineating the relative risk associated with multiple variables and understanding the multifactorial nature of post-operative complications in these patients. There are however, some limitations to our study. We exclusively included patients undergoing flap reconstruction and so no direct comparison can be made to patients undergoing primary closure, making it impossible to determine the contribution of reconstructive surgery to the complications observed. In addition, complications were considered collectively for the purpose of statistical analysis, so specific predictors of individual complications were not identified. With further development, however, this data may form the basis for a disease-specific risk calculator that can improve individualized risk prediction and enhance pre-operative counselling and planning.

Conclusion

This study identifies important risk factors for complications following flap reconstruction of sarcoma defects. The importance of patient, tumour and treatment-related variables is recognized with significant synergistic interaction between patient and tumour variables.

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4

CHAPTER 5

Flap reconstruction does not increase complication rates following surgical resection of extremity soft tissue sarcoma

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Abstract

Background: Flap reconstruction plays an essential role in the surgical management of extremity soft tissue sarcoma (ESTS) for many patients. But flaps increase the duration and complexity of the surgery and their contribution to overall morbidity is unclear. This study directly compares the complication rates in patients with ESTS undergoing either flap reconstruction or primary wound closure and explores contributing factors.

Methods: Eight hundred and ninety-seven patients who underwent ESTS resection followed by primary closure (631) or flap reconstruction (266) were included in this study. Data on patient, tumour and treatment variables and post-operative medical and surgical complications were collected. Univariate and multivariate regression analyses were performed to identify independent predictors of complications.

Results: Post-operative complications occurred in 33% of patients. Flap patients were significantly older, had more advanced disease and were more likely to require neoadjuvant chemo- and radiotherapy. There was no significant difference in complication rates following flap reconstruction compared to primary closure on multivariate analysis (38 vs 30.9% OR 1.12, CI 0.77-1.64, p=0.53). Pre-operative radiation and distal lower extremity tumour location were significant risk factors in patients who underwent primary wound closure but not in those who had flap reconstruction. Patients with comorbidities, increased BMI and systemic disease were at increased risk of complications following flap reconstruction.

Conclusions: Flap reconstruction is not associated with increased post-operative complications following ESTS resection. Flaps may mitigate the effects of some risk factors in selected patients.

Key Words: Soft tissue sarcoma, flap reconstruction, complications

Introduction

Soft tissue sarcomas are a diverse group of neoplasms that account for approximately 1% of adult malignancies. They most commonly involve the extremities and surgical management centres on achieving wide local excision to reduce local recurrences.[1,2] Use of pedicled or free flaps can provide coverage of vital structures and prostheses, permitting oncologically effective surgical resections while maximising functional outcomes.[3-5] Advances in reconstructive techniques have increased the number of patients in whom limb salvage can be safely achieved.[6,7]

While soft tissue reconstruction plays an essential role in the management of patients with extremity soft tissue sarcomas (ESTS), the contribution to post-operative morbidity remains controversial. As soft tissue reconstruction increases the complexity of the procedure and extends the operative and recovery time it might also be expected to increase post-operative complication rates. Conversely flaps import well vascularised tissue, which provides beneficial effects for wound healing.[8] Although some previous studies have reported that reconstructions are associated with increased adverse events[9-11] others suggest that flaps do not affect morbidity rates[12-14] or may actually reduce the rate of wound healing problems in high-risk cases.[15] Similarly the role of other variables in the development of post-operative complications in these patients is poorly understood with significant disagreement between studies. This lack of clarity poses a challenge for pre-operative patient counselling and the provision of accurate risk assessment.

This study directly compares the complication rates of patients with ESTS who underwent flap reconstruction to those who had primary wound closure in a large consecutive series at a single major tertiary referral centre. We also examine the specific risk factors that contribute to the development of complications in these respective groups.

Methods

Institutional research ethics board approval was obtained for this study. Patients who underwent surgical resection of ESTS followed by either primary closure or immediate (pedicled or free) flap reconstruction between January 2006 and January 2015 were identified from a prospectively maintained institutional database. Patients who were treated with skin grafts or local skin flaps alone or primary amputation of the limb were excluded.

Details of patient characteristics (age, sex, body mass index [BMI], smoking status), comorbidities (any documented disease including cardiovascular, pulmonary, haematological, endocrine, renal or liver condition), tumour variables (location, depth, diameter, volume, stage and grade), operative details (primary or secondary excision, reconstruction) and adjuvant therapies (radiation and chemotherapy) were collected from the database and retrospective chart review.

All post-operative surgical and medical complications occurring within 120 days of surgery were collected and categorised. Major surgical complications were defined as those requiring return to the operating room, admission for intravenous antibiotics or prolonged wound care beyond 120 days post-operatively. Minor surgical complications included non-surgical drainage of seroma or hematoma, oral antibiotics and prolonged wound care completed within 120 days of surgery.

Medical complications were classified according to the Clavien-Dindo grading system.[16] Minor medical complications included those that resulted in deviation from the normal post-operative course but did not need intervention (Grade I) and those requiring pharmacological treatment (Grade II). Major medical complications included those requiring invasive endoscopic, radiological or surgical procedures (Grade III) and life threatening complications necessitating admission to the Intensive Care (Grade IV).

Statistical analysis

Statistical analyses were performed using STATA/SE version 12.0 (StataCorp, Texas USA). The frequency of all categorical variables and the mean, standard deviation and range of all continuous variables were measured. Differences between patients who had primary closure and those who required flap reconstruction were determined using Chi-squared and Fischer's exact tests. Univariate analysis was performed to determine the association between variables and post-operative complications. Variables with significant association with complications on univariate analysis were included in the multivariate logistic regression model to determine independent predictors of complications. Univariate and multivariate models stratifying for method of closure and pre-operative radiation were also constructed. The Hosmer-Lemeshow test was used to determine the goodness of fit of the models. P-values <0.05 were considered statistically significant.

Results

Eight hundred and ninety-seven patients who underwent ESTS resection were eligible for inclusion in the study. Six hundred and thirty-one patients (70.3%) had primary closure while 266 (29.7%) had flap reconstruction. In patients requiring flap reconstructions, pedicled flaps were performed in 195 (73.3%) patients and free flaps were performed in 71 (16.7%) patients. The mean patient age was 56 years (range 18-97) and the mean BMI was 26.94 (range 15-57). Ninety three percent of cases presented with a primary tumour while 7% had a local recurrence. Seventy one percent of tumours were located in the lower limb with 68% deep to fascia and the mean tumour diameter was 9.3cm (range 0.4-45 cm). The majority of patients (54%) received neoadjuvant radiotherapy, which was administered in 25 daily fractions of 2Gy over a 5-week period and was completed 4 to 6 weeks prior to surgery. The differences between patient and tumour variables in the primary closure and flap reconstruction groups are illustrated in Table 1.

TABLE 1

Differences in patient and tumour characteristics in patients receiving reconstruction or primary closure

Patient/tumour characteristic		**Primary closure n=631 n (%)**	**Flap reconstruction n=266 n (%)**	**p-value**
Age (years)	Mean (±SD)	54.8 (17.1)	59.2 (18.6)	**0.001**
	≤45	197 (31.2)	60 (22.6)	**<0.009**
	45-55	127 (20.1)	46 (17.3)	0.33
	56-69	171 (27.1)	82 (30.8)	0.26
	≥70	136 (21.6)	78 (29.3)	**0.013**
Sex	Female	285 (45.2)	121 (45.5)	0.93
	Male	346 (54.8)	145 (54.5)	
Comorbidities	No	346 (54.8)	134 (50.4)	0.22
	Yes	285 (45.2)	132 (49.6)	
Smoker	No	549 (87.0)	223 (83.8)	0.21
	Yes	82 (13.0)	43 (16.2)	
Body mass index (kg/m^2)	<25	233 (38.4)	107 (42.5)	0.35
	25-29	213 (35.1)	97 (38.5)	0.44
	≥30	161 (26.5)	48 (19.0)	**0.016**
Prior surgery	No	474 (75.1)	193 (72.6)	0.42
	Yes	157 (24.9)	73 (27.4)	
Localisation	Upper extremity	175 (27.7)	85 (31.9)	0.20
	Lower extremity	456 (72.3)	181 (68.1)	
Lower extremity localisation	Proximal	387 (84.9)	108 (59.7)	**<0.001**
	Distal	69 (15.1)	73 (40.3)	
Upper extremity localisation	Proximal	144 (82.3)	49 (57.6)	**<0.001**
	Distal	31 (17.7)	36 (42.4)	

- Table 1 continued -

Patient/tumour characteristic		Primary closure n=631 n (%)	Flap reconstruction n=266 n (%)	p-value
Maximal tumour diameter (cm)	<10	399 (63.5)	181 (69.1)	0.11
	≥10	229 (36.5)	81 (30.9)	
Tumour volume (cm^3 or ml)	Mean (±SD)	819.2 (192.8)	686.8 (151.3)	0.34
	<35.0	160 (27.6)	48 (19.8)	**0.018**
	35-149	117 (20.2)	82 (33.7)	**<0.001**
	150-649	143 (24.7)	59 (24.3)	0.88
	≥650	160 (27.6)	54 (22.2)	0.11
Tumour stage	I	197 (31.4)	59 (22.4)	**0.006**
	II	273 (43.5)	95 (36.1)	**0.036**
	III	118 (18.8)	82 (31.2)	**<0.001**
	IV	39 (6.2)	27 (10.3)	**0.038**
Tumour depth	Deep	437 (69.3)	174 (65.4)	0.26
	Superficial	194 (30.7)	92 (34.6)	
Pre-operative radiotherapy	No	341 (54.0)	69 (25.9)	**<0.001**
	Yes	290 (46.0)	197 (74.1)	
Post-operative radiotherapy	No	601 (95.3)	241 (90.06)	**0.008**
	Yes	30 (4.7)	25 (9.4)	
Pre-operative chemotherapy	No	604 (96.2)	242 (91.0)	**0.002**
	Yes	24 (3.8)	24 (9.0)	

Patients in the flap reconstruction group were significantly older (59.2 +/- 18.6 vs. 54.8 +/- 17.1 years, p=0.001), their tumours were more likely to be located in the distal extremities, and were more likely to have more advanced disease (stage III or IV) that required radiation and chemotherapy in addition to surgery.

The overall post-operative complication rate was 33% in this series. Major surgical complications occurred in 10.7% of patients. Almost 20% of patients experienced minor surgical complications that did not require further surgery. Both major and minor medical complications were rare occurring in 0.9% and 1.7% of cases respectively. A number of variables were associated with increased complication rates on univariate analysis (increased age and BMI, comorbidities, lower limb tumours, large and deep tumours, prior surgery, advanced stage, flap reconstruction and pre-operative radiation) and were included in the multivariate model (Table 2). Only four of these factors, increased BMI (≥30, OR 1.79,95% CI 1.17-2.74, p=0.007), lower limb tumour location (OR 2.10, 95% CI 1.41-3.12, p<0.001), stage IV disease (OR 2.28, 95% CI 1.07-4.86, p=0.03) and pre-operative radiation (OR 2.66, 95% CI 1.83-3.87, p<0.001) were confirmed to be independent predictors of complications on multivariate analysis. Patients with flap reconstructions had higher rates of both overall and specific complications based on univariate analysis but this was not significant on multivariate modeling (Table 3).

TABLE 2

Complication rates according to patient and tumour characteristics and multivariate logistic regression analyses

Patient/tumour characteristic	Complications %	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Surgery					
Primary closure	30.9	1.0 (ref)		1.0 (ref)	
Flap reconstruction	38.0	1.37 (1.01-1.85)	**0.04**	1.12 (0.77-1.64)	0.53
Age (years)					
≤45	31.5	1.0 (ref)		1.0 (ref)	
45-55	26.6	0.79 (0.51-1.21)	0.27	0.65 (0.39-1.07)	0.09
56-69	30.0	0.93 (0.64-1.36)	0.72	0.79 (0.50-1.24)	0.30
70+	43.5	1.67 (1.15-2.44)	**0.008**	1.30 (0.78-2.16)	0.32
Sex					
Female	32.0	1.0 (ref)			
Male	33.8	1.08 (0.82-1.43)	0.57		
Comorbidities					
No	28.8	1.0 (ref)		1.0 (ref)	
Yes	37.9	1.51 (1.14-2.00)	**0.004**	1.23 (0.85-1.79)	0.28
Smoker					
No	32.5	1.0 (ref)			
Yes	36.0	1.17 (0.79-1.73)	0.44		
Body mass index (kg/m^2)*					
<25	27.4	1.0 (ref)		1.0 (ref)	
25-29	35.2	1.44 (1.03-2.01)	**0.03**	1.47 (1.01-2.14)	**0.04**
≥30	37.8	1.61 (1.12-2.33)	**0.01**	1.79 (1.17-2.74)	**0.007**
Prior surgery					
No	36.0	1.0 (ref)		1.0 (ref)	
Yes	24.4	0.57 (0.41-0.80)	**0.001**	1.16 (0.71-1.89)	0.56
Localisation					
Upper extremity	20.0	1.0 (ref)		1.0 (ref)	
Lower extremity	38.3	2.48 (1.76-3.50)	**<0.001**	2.10 (1.41-3.12)	**<0.001**
Localisation lower extremity					
Lower proximal	36.4	1.0 (ref)			
Lower distal	45.1	1.44 (0.98-2.10)	0.06		
Localisation upper extremity					
Upper proximal	17.6	1.0 (ref)			
Upper distal	26.9	1.72 (0.89-3.31)	0.11		
Depth					
Deep	37.5	1.0 (ref)		1.0 (ref)	
Superficial	23.4	0.51 (0.37-0.70)	**<0.001**	0.87 (0.51-1.48)	0.60
Maximum size tumour (cm)*					
<10	29.1	1.0 (ref)		1.0 (ref)	
≥10	40.7	1.67 (1.25-2.22)	**0.001**	1.02 (0.56-1.87)	0.95

- Table 2 continued -

Patient/tumour characteristic	Complications %	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Tumour volume (cm^3 or ml)					
<35.0	24.0	1.0 (ref)		1.0 (ref)	
35.0-149	30.2	1.36 (0.88-2.12)	0.17	0.87 (0.51-1.50)	0.62
150-649	38.6	1.99 (1.30-3.04)	**0.002**	1.20 (0.64-2.23)	0.57
≥650	41.6	2.25 (1.48-3.42)	**<0.001**	1.37 (0.60-3.13)	0.46
Stage*					
I	21.9	1.0 (ref)		1.0 (ref)	
II	33.4	1.79 (1.24-2.59)	**0.002**	1.15 (0.67-1.98)	0.62
III	40.5	2.43 (1.61-3.66)	**<0.001**	1.16 (0.61-2.21)	0.66
IV	53.0	4.03 (2.29-7.11)	**<0.001**	2.28 (1.07-4.86)	**0.03**
Pre-operative radiotherapy					
No	22.0	1.0 (ref)		1.0 (ref)	
Yes	42.3	2.61 (1.94-3.50)	**<0.001**	2.66 (1.83-3.87)	**<0.001**
Post-operative radiotherapy					
No	32.7	1.0 (ref)			
Yes	38.2	1.27 (0.73-2.24)	0.40		
Pre-operative chemotherapy					
No	33.0	1.0 (ref)			
Yes	33.3	1.02 (0.55-1.88)	0.96		

Ref=reference category

* Missing cases were excluded for analyses

Pre-operative radiation was found to be the strongest independent predictor of complications in the patient cohort (OR 2.66, 95% CI 1.83-3.87, p<0.001; Table 2). Patients in both the primary closure and flap groups were therefore stratified for pre-operative radiation in further multivariate logistic regression analyses (Table 4). In the primary closure group patients who received pre-operative radiation had a significantly higher rate of complications compared to those who did not (44.1 vs 19.7%, OR 3.87, 95% CI 2.32-6.45, p<0.001). In the flap reconstruction group however, there was no significant association between complications and pre-operative radiation (OR 0.72, 95% CI 0.38-1.34, p=0.55).

These results suggest that the predictors of complications differed between the two wound closure treatment groups, which lead us to perform separate univariate and multivariate regression analyses for patients with primary closure and flap reconstructions (Table 5). In the primary closure group tumours of the distal lower extremity (OR 1.99, 95% CI 0.12-3.53, p=0.02) and pre-operative radiation (OR 3.91, 95% CI 2.34-6.54, p<0.001) were found to be independent predictors of complications. In the flap reconstruction group stage IV disease was the strongest predictor of complications (OR 4.51, 95% CI

TABLE 3

Univariate and multivariate comparisons of medical and surgical complications observed in the flap reconstruction and primary closure groups

Complication Type	Overall	Reconstruction Group	Primary Closure Group	Univariate p-value	Adjusted OR* (95% CI)	Multivariate p-value
All Complications	33%	38%	31%	0.04	0.99 (0.69-1.42)	0.96
Major Surgical	10.7%	14.7%	9.0%	0.01	0.74 (0.44-1.24)	0.25
Minor Surgical	19.8%	19.9%	19.3%	0.94	1.19 (0.78-1.83)	0.42
Major Medical	0.9%	2.6%	1.1%	0.10	0.74 (0.21-2.56)	0.64
Minor Medical	1.7%	3.1%	1.1%	0.07	0.62 (0.26-1.44)	0.27

*Models adjusted for prior surgery, comorbidities, BMI, tumour localisation, tumour depth, tumour size, tumour stage and pre-operative radiotherapy.

TABLE 4

Complication rate according to type of surgery and stratified for pre-operative radiation therapy-multivariate logistic regression analyses

Factor	Complications %	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Primary closure					
No radiotherapy	19.7	1.0 (ref)	**<0.001**	1.0 (ref)	**<0.001**
Pre-operative radiation	44.1	3.23 (2.27-4.60)		3.87 (2.32-6.45)[a]	
Reconstruction					
No radiotherapy	33.3	1.0 (ref)	0.36	1.0 (ref)	0.55
Pre-operative radiation	39.6	0.76 (0.43-1.36)		0.72 (0.38-1.34)[b]	

Ref=reference category
[a] Adjusted for comorbidity, localisation lower extremities, depth, size, volume and stage
[b] Adjusted for comorbidity, BMI and stage

1.61-12.58, p=0.004). Comorbidities and BMI ≥30 were also significantly associated with complications following flap reconstruction (OR 1.75, 95% CI 1.01-3.04, p=0.048 and OR 2.35, 95% CI 1.12-4.93, p=0.02 respectively).

Discussion

To our knowledge, this is the largest series examining complications following ESTS resection and the first study to comprehensively explore the specific risk factors associated with primary closure and flap reconstructions. The overall complication rate was relatively high with almost one third of patients experiencing an adverse post-operative event, which is largely in keeping with previous reports and reflects the complexity of limb salvage procedures in patients with ESTS.[9-11,15]

TABLE 5

Univariate and multivariate logistic regression analyses for independent risk factors of complications - stratified for method of wound closure

Patient/tumour characteristic		Primary closure				Flap reconstruction			
		Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value	Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Sex	Female	1.0 (ref)				1.0 (ref)			
	Male	1.06 (0.76-1.49)	0.72			1.13 (0.69-1.87)	0.62		
Body mass index (kg/m^2)	<25	1.0 (ref)				1.0 (ref)		1.0 (ref)	
	25-29	1.21 (0.81-1.82)	0.36			2.05 (1.14-3.69)	**0.02**	1.77 (0.95-3.27)	0.07
	≥30	1.45 (0.94-2.23)	0.10			2.28 (1.12-4.63)	**0.02**	2.35 (1.12-4.93)	**0.02**
Comorbidities	No	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
	Yes	1.43 (1.02-2.00)	**0.04**	1.27 (0.78-2.08)	0.34	1.66 (1.01-2.73)	**0.047**	1.75 (1.01-3.04)	**0.048**
Smoker	No	1.0 (ref)				1.0 (ref)			
	Yes	0.98 (0.59-1.62)	0.93			1.52 (0.79-2.94)	0.21		
Age (years)	≤45	1.0 (ref)		1.0 (ref)		1.0 (ref)			
	45-55	0.77 (0.47-1.27)	0.31	0.88 (0.46-1.66)	0.69	0.81 (0.36-1.85)	0.62		
	56-69	0.87 (0.55-1.36)	0.53	1.06 (0.58-1.94)	0.84	1.02 (0.51-2.04)	0.96		
	70+	1.60 (1.01-2.52)	**0.04**	1.54 (0.78-3.03)	0.21	1.68 (0.84-3.35)	0.14		
Prior surgery	No	1.0 (ref)		1.0 (ref)		1.0 (ref)			
	Yes	0.47 (0.30-0.72)	**0.001**	1.19 (0.52-2.70)	0.68	0.80 (0.46-1.41)	0.44		
Upper extremity localisation	Proximal	1.0 (ref)				1.0 (ref)			
	Distal	1.13 (0.39-3.26)	0.83			1.57 (0.62-3.97)	0.35		
Lower extremity localisation	Proximal	1.0 (ref)		1.0 (ref)		1.0 (ref)			
	Distal	1.94 (1.16-3.26)	**0.01**	1.99 (0.12-3.53)	**0.02**	0.89 (0.49-1.63)	0.70		
Tumour stage	I	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
	II	2.09 (1.36-3.23)	**0.001**	0.95 (0.41-2.19)	0.90	1.16 (0.58-2.33)	0.68	1.11 (0.53-2.31)	0.78
	III	2.77 (1.66-4.62)	**<0.001**	0.82 (0.32-2.10)	0.67	1.61 (0.80-3.27)	0.19	1.63 (0.77-3.46)	0.20
	IV	3.59 (1.74-7.38)	**0.001**	1.27 (0.43-3.80)	0.67	3.87 (1.49-10.09)	**0.006**	4.51 (1.61-12.58)	**0.004**
Tumour depth	Deep	1.0 (ref)		1.0 (ref)		1.0 (ref)			
	Superficial	0.40 (0.26-0.60)	**<0.001**	1.05 (0.42-2.64)	0.91	0.76 (0.45-1.28)	0.30		
Maximal tumour diameter (cm)	<10	1.0 (ref)		1.0 (ref)		1.0 (ref)			
	≥10	1.84 (1.30-2.60)	**0.001**	0.92 (0.42-2.03)	0.85	1.43 (0.84-2.43)	0.19		
Pre-operative radiotherapy	No	1.0 (ref)		1.0 (ref)		1.0 (ref)			
	Yes	3.23 (2.27-4.60)	**<0.001**	3.91 (2.34-6.54)	**<0.001**	1.31 (0.74-2.33)	0.36		
Post-operative radiotherapy	No	1.0 (ref)				1.0 (ref)			
	Yes	1.52 (0.72-3.23)	0.27			0.91 (0.39-2.15)	0.83		
Pre-operative chemotherapy	No	1.0 (ref)				1.0 (ref)			
	Yes	1.36 (0.58-3.16)	0.48			0.65 (0.26-1.62)	0.35		

Direct comparison with other studies is difficult due to the variation in the outcomes analysed in previous papers. The majority of studies focus only on major wound complications while we considered all surgical and medical complications occurring within 120 days of surgery. While most studies continue to use the criteria described by O'Sullivan *et al*. to define major wound complications we applied some modification of these to reflect changes in modern wound management.[17]

We considered seromas that did not require readmission or surgical drainage to be minor complications. Similarly use of vacuum assisted closure devices on an outpatient basis, which were not utilized in the O'Sullivan study, precluded the need for readmission and prolonged wound packing in many patients in this study and these cases were also classified as minor complications.

Increased BMI, stage IV disease, lower extremity tumours and pre-operative radiation were all identified as independent predictors of complications in the study group as a whole. Although we observed an increased rate of complications in patients with flap reconstruction compared to primary wound closure (38% vs. 31% respectively), this difference was only significant on univariate but not multivariate analysis (Table 2). Patients who had flap reconstruction could be considered at higher risk as they were significantly older with more advanced disease (stage III or IV) and were also more likely to have tumours of the distal extremity and need pre-operative radiation and chemotherapy, all of which may have contributed to the trend toward higher complication rates in this group. Flap reconstruction was not an independent predictor of complications.

Perhaps the most important finding of this study is that predictors of complications are different following primary wound closure and flap reconstructions. Interestingly, pre-operative radiation, which was the strongest predictor in the group as a whole, was not associated with the risk of complications following flap reconstruction. As flap reconstruction imports healthy, well-vascularised tissue that has not been affected by prior treatments it may mitigate the adverse effects of radiation on wound healing. In support of this finding, defects of the distal lower extremity were not associated with increased complications in the flap reconstruction group where the addition of healthy tissues may facilitate more robust tension free closure. Conversely, comorbidities, increased BMI and the presence of metastatic disease were associated with increased complications following flap reconstruction but did not affect outcomes in the primary closure group. Extended operative procedures may be less well tolerated by patients with significant comorbidities, resulting in higher rates of complications following flap

reconstruction.[17] In addition comorbidities including diabetes and obesity are known to compromise wound healing at both the donor and recipient sites following complex reconstructive surgery.[18-21] In this study we considered complications collectively and so any association between risk factors and specific medical or surgical complications could not be determined.

This comprehensive analysis of factors contributing to complications provides important information for pre-operative assessment and counselling of patients undergoing surgical resection of ESTS. With increasing emphasis on personalised cancer care it is no longer sufficient to simply list possible complications of treatment.[22] The Institute of Medicine has identified the provision of information on treatment benefits and harm as a key priority in the delivery of high quality cancer care and so there is growing demand for individualised pre-operative risk assessment.[23] In order to provide this, surgeons must have a clear understanding of the factors that contribute to adverse outcomes in specific patient populations.[24]

In the majority of patients in this study, the decision to perform flap reconstruction was mandated by the size of the defect following sarcoma resection or exposure of vital structures. However in some cases although it may have been possible to close the wound primarily, it was preferable to reconstruct the soft tissue defect with a flap. The results of this study suggest this may be the case particularly in radiated patients and those with tumours of the lower leg where wound closure under tension may be especially prone to failure. However, in patients with comorbidities, obesity or metastatic disease the possible benefits of flap reconstruction must be weighed against the increased risk of complications. Further study is required to quantify the relative importance of these risk factors so that an appropriate balance can be achieved related to decision-making in each individual patient.

The experience of both the orthopaedic oncologist and the plastic surgeon is critical in the shared decision-making process. This study was conducted at a high volume tertiary referral centre with a dedicated multidisciplinary sarcoma team where the accessibility of plastic surgery services may have lowered our threshold for performing flap reconstructions. In addition pre-operative radiation is the modality of choice at our centre and so we have extensive experience using flap reconstruction in a recently radiated field.[25] We acknowledge that our findings may not be replicated in other institutions that follow different treatment protocols.

Although this study included a large number of variables it is not exhaustive. Other

factors such as tumour type, flap type or complexity of the ablative procedure may also influence outcomes but the heterogeneous nature of ESTS makes it difficult to consider all possible variables.[12,26-28] This study only included complications occurring within the early post-operative period and has not considered late complications or long term functional outcomes, which are also critical to pre-operative planning. However, previous reports from our centre suggest that flap reconstruction does not adversely affect post-operative function or health status outcomes in ESTS patients.[28] Although most of the data included in this study was collected prospectively some clinical details were obtained through retrospective chart review, which may have resulted in some bias. In addition the study groups were not matched and there was significant differences in baseline characteristics, which may have affected the findings.

Conclusions

Flap reconstruction does not increase complication rates following ESTS resection. Use of flaps may mitigate the effect of some risk factors such as pre-operative radiation or distal leg location but patients with increased BMI, comorbidities or advanced disease stage may be at increased risk of complications following these more complex procedures.

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CHAPTER 6

Flap choice does not affect complication rates or functional outcomes following extremity soft tissue sarcoma reconstruction

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Abstract

Background: Flap reconstruction plays an essential role in facilitating limb preservation in patients with extremity soft tissue sarcoma (ESTS). However, the effect of flap choice on the rates of post-operative complications and functional outcomes has not been clearly established. This study directly compares the outcomes of free and pedicled flap reconstructions in patients with ESTS.

Methods: Two hundred and sixty-six patients who underwent flap reconstruction following ESTS resection were included. Associations between flap type and complications were determined using logistic regression analyses. Functional outcome was evaluated using the Toronto Extremity Salvage Score (TESS) and the Musculoskeletal Tumor Society Scales (MSTS).

Results: There was no significant difference between complication rates in the pedicled and free flap groups (32% vs 38%, p=0.38). In the lower limb pedicled flaps had complication rates similar to those of free flaps on univariate analysis (odds ratio [OR] =1.12, 95% confidence interval [CI] =0.56-2.26, p=0.75). Conversely in the upper limb pedicled flaps were associated with fewer complications on univariate analysis (OR 0.31, 95%CI 0.11-0.86, p=0.03), but this was not significant on multivariate analysis (OR 0.45, 95%CI 0.13-1.59, p=0.22). Obesity was a strong predictor of complications in the upper limb group on multivariate analysis (body mass index [BMI] ≥30 kg/m^2 OR 7.01, 95%CI 1.28-38.51, p=0.03). There was no significant difference in functional outcomes between both flap groups in either upper or lower limbs.

Conclusions: Post-operative complications and functional outcomes for patients undergoing free and pedicled flaps are similar in ESTS reconstruction. Selecting the most suitable reconstructive option in each individual case is paramount to preserving function while minimizing post-operative morbidity.

Key Words: Extremity soft tissue sarcoma, reconstruction, free flap, pedicled flap.

Introduction

Soft tissue sarcomas are rare heterogeneous neoplasms that commonly involve the extremities. Historically these patients were treated by amputation but improvements in surgical techniques, radiological imaging and adjuvant therapies have now made limb preservation possible in the majority of cases.[1,2] Multidisciplinary management of patients with extremity soft tissue sarcoma (ESTS) frequently involves both wide resection to achieve clear margins and (neo)adjuvant radiation to minimize local recurrence. In many cases this results in extensive soft tissue defects that cannot be managed using simple wound closure or skin grafting techniques. Reconstruction using pedicled or free flaps is therefore often necessary to provide coverage of vital structures or prostheses and facilitate limb preservation.

We previously reported that while flap reconstruction increases the complexity of surgery it does not significantly increase post-operative complication rates in ESTS patients.[3] However, the effect of the choice of flap on post-operative morbidity has not been clearly established in this patient population. As free flaps require microvascular anastomosis they may be perceived to be more complicated and therefore associated with higher risks of complications. On the other hand pedicled flaps often involve extensive surgical dissection adjacent to the zone of tumour ablation which might adversely affect functional outcomes. Reports in extremity trauma patients suggest that post-operative outcomes of free and pedicled flaps are similar.[4-6] However this may not necessarily be the case following ESTS resection as the patient population is more heterogenous and variables such as older age and comorbidities may affect outcomes.[7,8] In addition adjuvant treatments such as chemotherapy and particularly neoadjuvant radiation must be considered in oncological reconstruction.[9-11]

This study compares the complication rates and functional outcomes of free and pedicled flap reconstructions in a large cohort of patients with ESTS at a single major tertiary referral centre.

Methods

Institutional Research Ethics Board approval was obtained for this study. Patients who underwent resection of a soft tissue sarcoma of the upper or lower extremity and required either free or pedicled flap reconstruction between January 2006 and January 2015 were identified from a prospectively maintained database at Mount Sinai Hospital, Toronto, Canada. Patient demographics (age, sex, body mass index [BMI],

smoking status, comorbidities), tumour characteristics (histology, location, stage, grade, depth, diameter and volume), surgical details (primary or secondary resection, timing of reconstruction, reconstructive technique) and adjuvant therapies (radiation and chemotherapy) were recorded from the database and retrospective chart review.

All post-operative surgical complications occurring within 120 days of surgery were recorded and categorized. Major complications were defined as those requiring return to the operating room (OR), intravenous antibiotics or prolonged wound care beyond 120 days. Minor complications included those requiring oral antibiotics, non-surgical management of seroma or hematoma and wound care concluding within 120 days of surgery. Any complications that delayed delivery of adjuvant therapies were considered major.

Functional outcomes were assessed using three measurement tools; the Toronto Extremity Salvage Score (TESS) and the Musculoskeletal Tumor Society (MSTS) 87 and 93 rating scales. The TESS was specifically developed for extremity sarcoma patients and is a patient-reported outcome tool that measures performance on activities of daily living.[12,13] Twenty-nine items are rated from 0-5 with higher scores indicating better function. The MSTS 87 is a physician-derived assessment that evaluates seven aspects of joint function (mobility, pain, stability, deformity, strength, functional and emotional acceptance).[14] The MSTS 93 is a more limb-specific measure also assessed by physicians, that includes six domains of function (pain, function, emotional acceptance, positioning, dexterity and strength) to determine functional impairment.[15] The MSTS 87 and 93 systems both score each item from 0-5. The TESS and MSTS 93 total scores are expressed as a percentage. The MSTS 87 usually has a maximum score of 35, but for ease of comparability it was also expressed as a percentage. The differences between the pre-operative and post-operative (9-12 months) TESS, MSTS 87 and MSTS 93 scores were calculated and compared.

Statistical analysis

Statistical analyses were performed using STATA/SE version 12.0 (StataCorp, Texas, USA). Mean, standard deviation and range were calculated for all continuous variables. Differences between experimental groups were calculated using the t-test for continuous variables and Chi-squared or Fisher's exact test for categorical variables. Clinical factors associated with post-operative complications were identified using logistic regression analysis. For comparison of the functional scores between pedicled and free flap reconstruction patient groups, the Mann-Whitney test was used. P-values ≤ 0.05 were considered statistically significant.

Results

Two hundred and sixty six patients who underwent ESTS resection followed by reconstruction with a free or pedicled flap were evaluated in this study. There were 145 (55%) male and 121 (46%) female patients with mean age of 59.2 (standard deviation [SD] ±18.6) years and mean BMI of 26.4 (SD ±5.7). One hundred and thirty two patients (50%) had comorbidities and 43 (16%) were smokers. Pre-operative radiation therapy was administered in 197 patients (74%). One hundred and seventy four patients (65%) had deep tumours, indicating that they were deep to or involved the deep fascia. The majority of patients presented with a primary tumour (92%) and the mean tumour diameter was 9.01 ±6.1cm. All patient and tumour variables are outlined in Table 1.

TABLE 1

Differences in patient, tumour and treatment characteristics between free and pedicled flaps in upper and lower limb ESTS patients

			Lower limb, n=181 (68.1%)			Upper limb, n=85 (31.9%)		
Characteristic		**n (%)**	**Free (n=45)**	**Pedicled (n=136)**	**p-value**	**Free (n=26)**	**Pedicled (n=59)**	**p-value**
Age (years)	Mean ± SD	59.18(18.59)	55.4 (17.9)	60.7 (19.1)	0.18	53.5 (15.2)	61.1 (17.9)	0.059
	≤45	60 (22.6)	15 (33.3)	28 (20.6)	0.07	6 (23.1)	11 (18.6)	0.16
	45-55	46 (17.3)	4 (8.9)	24 (17.7)		8 (30.8)	10 (17.0)	
	56-69	82 (30.8)	17 (37.8)	38 (27.9)		9 (34.6)	18 (30.5)	
	70+	78 (29.3)	9 (20.0)	46 (33.8)		3 (11.5)	20 (33.9)	
Sex	Female	121 (45.5)	22 (48.9)	66 (48.5)	0.97	11 (42.3)	22 (37.3)	0.66
	Male	145 (54.5)	23 (51.1)	70 (51.5)		15 (57.7)	37 (62.7)	
Comorbidities	No	134 (50.4)	23 (51.1)	64 (47.1)	0.64	16 (61.5)	31 (52.5)	0.44
	Yes	132 (49.6)	22 (48.9)	72 (52.9)		10 (38.5)	28 (47.5)	
Smoker	No	223 (83.8)	39 (86.7)	119 (87.5)	0.88	18 (69.2)	47 (79.7)	0.30
	Yes	43 (16.2)	6 (13.3)	17 (12.5)		8 (30.8)	12 (20.3)	
BMI*	Mean ± SD	26.35 (5.65)	27.6 (6.3)	26.2 (5.8)	0.25	27.9 (4.8)	24.9 (4.8)	**0.007**
	<25	107 (40.2)	18 (40.0)	54 (44.3)	0.39	6 (23.1)	29 (49.2)	0.06
	25-29	97 (36.5)	15 (33.3)	47 (38.5)		13 (50.0)	22 (37.3)	
	≥30	48 (18)	12 (26.7)	21 (17.2)		7 (26.9)	8 (13.6)	
Presenting status	Primary	245 (92.1)	41 (24.4)	127 (75.6)	0.61	24 (31.2)	53 (68.8)	0.72
	LR	21 (7.9)	4 (30.8)	9 (69.2)		2 (25.0)	6 (75.0)	
Prior surgery	No	193 (72.6)	29 (64.4)	107 (78.7)	0.06	19 (73.1)	38 (64.4)	0.43
	Yes	73 (27.4)	16 (35.6)	29 (21.3)		7 (26.9)	21 (35.6)	
Localisation	Proximal	157 (59.1)	17 (37.8)	91 (66.9)	**0.001**	14 (53.9)	35 (59.3)	0.64
	Distal	109 (40.9)	28 (62.2)	45 (33.1)		12 (46.1)	24 (40.7)	
Maximal tumour diameter (cm)*	Mean ± SD	9.01 (6.1)	10.67 (8.7)	9.33 (5.8)	0.91	9.28 (5.7)	6.95 (3.6)	0.27
	<10	181 (68)	31 (72.1)	87 (64.4)	0.36	14 (53.9)	49 (84.5)	**0.003**
	≥10	81 (30.5)	12 (27.9)	48 (35.6)		12 (46.1)	9 (15.5)	

- Table 1 continued -

Characteristic		n (%)	Lower limb, n=181 (68.1%)			Upper limb, n=85 (31.9%)		
			Free (n=45)	Pedicled (n=136)	p-value	Free (n=26)	Pedicled (n=59)	p-value
Tumour volume* (cm^3 or ml)	<35.0	48 (18)	2 (5.4)	21 (16.5)	0.11	9 (34.6)	16 (30.2)	**0.02**
	35.0-149	82 (30.8)	19 (51.4)	40 (31.5)		4 (15.4)	19 (35.9)	
	150-649	59 (22.2)	8 (21.6)	34 (26.8)		4 (15.4)	13 (24.5)	
	≥650	54 (20.3)	8 (21.6)	32 (25.2)		9 (34.6)	5 (9.4)	
Tumour depth	Deep	174 (65.4)	27 (60.0)	90 (66.2)	0.45	24 (92.3)	33 (55.9)	**0.001**
	Superficial	92 (34.6)	18 (40.0)	46 (33.8)		2 (7.7)	26 (44.1)	
Tumour stage*	I	59 (22.2)	11 (25.0)	31 (23.0)	0.19	5 (19.2)	12 (20.7)	0.97
	II	95 (35.7)	14 (31.8)	44 (32.6)		11 (42.3)	26 (44.8)	
	III	82 (30.8)	10 (22.7)	47 (34.8)		8 (30.8)	17 (29.3)	
	IV	27 (10.2)	9 (20.5)	13 (9.6)		2 (7.7)	3 (5.2)	
Pre-operative radiotherapy	No	69 (25.9)	7 (15.6)	36 (26.5)	0.14	5 (19.2)	21 (35.6)	0.13
	Yes	197 (74.1)	38 (84.4)	100 (73.5)		21 (80.8)	38 (64.4)	
Post-operative radiotherapy	No	241 (90.6)	43 (95.6)	121 (89.0)	0.19	24 (92.3)	53 (89.8)	0.72
	Yes	25 (9.4)	2 (4.4)	15 (11.0)		2 (7.7)	6 (10.2)	
Pre-operative chemotherapy	No	242 (91)	40 (88.9)	122 (89.7)	0.88	26 (100)	54 (91.5)	0.13
	Yes	24 (9)	5 (11.1)	14 (10.3)		0 (0.0)	5 (8.5)	

BMI: Body mass index (kg/m^2) ; LR: Local recurrence

* Excluding missing values (BMI: 14, tumour size: 4, stage: 3)

Pedicled flaps were performed in 195 (73%) patients and consisted of 82 muscle flaps with split thickness skin graft, 64 musculocutaneous and 49 fasciocutaneous flaps. Free flaps were performed in 71 (17%) patients and consisted of 47 fasciocutaneous, 14 muscle with split thickness skin graft and 10 musclulocutaneous flaps. One hundred and eighty one patients (68%) had lower limb tumours and 136 of these had pedicled flap reconstruction whereas 45 had free flaps. Free flaps were significantly more common than pedicled flaps in patients with tumours distal to the knee (62% vs 33%, p=0.001). There was no other significant difference between the pedicled and free flap groups in lower limb ESTS. Eighty-five patients (32%) had tumours of the upper limb. Fifty-nine of these had pedicled flaps while 26 had free flap reconstructions. Free flaps were significantly more common than pedicled flaps when tumours were larger (46% vs 16% for tumour diameter ≥10cm, p=0.003; 34% vs 9% for tumour volume ≥ 650ml, p=0.02) and deep (92% vs 56%, p=0.001). Patients in the free flap group also had significantly higher mean BMI compared to pedicled flaps (27.9 ±4.8 vs 24.9 ±4.8, p=0.007) in upper limb cases. Differences between the free and pedicled flap groups in upper and lower extremity cases are outlined in Table 1. The flaps performed are listed in Table 2.

Post-operative surgical complications occurred in 90 (34%) patients, with 52 being classified as major (Table 3). There was no significant difference in complication rates

TABLE 2

Types of flaps used in the study cohort

Flap type	Pedicled flaps (n=195, 73.3%) n (% of total)	Free flaps (n=71, 26.7%) n (% of total)
Gastrocnemius	62 (23.3)	
Latissimus dorsi	29 (10.9)	12 (4.5)
Radial forearm	26 (9.8)	6 (2.3)
Sartorius	23 (8.6)	
Rectus abdominis	16 (6.0)	6 (2.3)
Anterolateral thigh	16 (6.0)	44 (16.5)
Perforator	7 (2.6)	
Gluteus maximus	3 (1.1)	
Soleus	3 (1.1)	
Pectoralis	2 (0.8)	
Gracilis	3 (1.1)	2 (0.8)
Tensor fascia lata	2 (0.8)	
Vastus lateralis	1 (0.4)	
Rectus femoris	1 (0.4)	
Semimembranosus	1 (0.4)	
Parascapular		1 (0.4)

between patients who underwent free or pedicled flaps (38% vs 32%, p=0.38). Flap reconstructions of the lower limb tended to have higher complication rates than those of the upper limb, but this did not reach statistical significance for either major (38% vs 26%, p=0.06) or minor complications (22% vs 14%, p=0.15).

Logistic regression analysis was used to examine whether flap type was a significant predictor of complications in patients with lower or upper ESTS (Table 4). In the lower limb, pedicled flaps had a slightly increased association with complications compared to free flaps but this was not significant (OR 1.12, 95% CI 0.56-2.26, p=0.75). Conversely in the upper limb pedicled flaps were associated with fewer complications on univariate analysis (OR 0.31, 95% CI 0.11-0.86, p=0.03). A multivariate model was therefore constructed and included other variables that, according to current literature, may affect post-operative complications rates. On multivariate analysis free flaps were no longer significantly associated with complications (OR 0.45, 95% CI 0.13-1.59, p=0.22). However, high BMI was a strong independent predictor of complications in the upper limb group on multivariate analysis (BMI ≥ 30 OR 7.01, 95% CI 1.28-38.51, p=0.03).

TABLE 3

Complications stratified for flap type and tumour location

Complication	Total (n=266)		Pedicled (n=195)		Free (n=71)		p-value	Lower limb (n=181)		Upper limb (n=85)		p-value
	n	%	n	%	n	%		n	%	n	%	
Minor surgical complications	38	14.3%	28	14.4%	11	15.5%	0.82	29	16%	10	11.8%	0.36
Infection	14	5.3%	10	5.1%	4	5.7%		12	6.6%	3	3.5%	
Wound dehiscence	13	4.9%	9	4.6%	4	5.7%		10	5.5%	3	3.5%	
Delayed wound healing	6	2.3%	5	2.6%	1	1.4%		5	2.8%	1	1.2%	
Seroma	1	0.4%	1	0.5%	-	-		1	0.6%	-	-	
Hematoma	1	0.4%	-	-	1	1.4%		-	-	1	1.2%	
Partial necrosis	3	1.1%	2	1.0%	1	1.4%		1	0.6%	2	2.4%	
Major surgical complications	52	19.5%	35	17.9%	16	22.5%	0.40	39	21.6%	12	14.1%	0.15
Infection requiring iv antibiotics	18	6.8%	14	7.2%	3	4.2%		16	8.8%	1	1.2%	
Delayed wound healing	6	2.3%	6	3.1%	-	-		5	2.8%	1	1.2%	
Wound dehiscence	5	1.9%	5	2.6%	-	-		5	2.8%	-	-	
Hematoma	3	1.1%	3	1.5%	-	-		2	1.1%	1	1.2%	
Partial necrosis	9	3.4%	3	1.5%	6	8.5%		6	3.3%	3	3.5%	
Flap compromise	4	1.5%	-	-	4	5.7%		1	0.6%	3	3.5%	
Flap failure	7	2.6%	4	2.1%	3	4.3%		4	2.2%	3	3.5%	
Total complications	90	33.8%	63	32.3%	27	38.0%	0.38	68	37.6%	22	25.9%	0.06

TABLE 4

Risk factors for complications

Factor		Univariate OR (95%CI)	p-value	Multivariate OR (95%CI)	p-value
Lower extremity[a]					
Flap	Free	1.0	0.75	-	-
	Pedicled	1.12 (0.56-2.26)			
Upper extremity[b]					
Flap	Free	1.0	**0.03**	1.0	0.22
	Pedicled	0.31 (0.11-0.86)		0.45 (0.13-1.59)	
Body mass index (kg/m^2)	<25	1.0 (ref)		1.0 (ref)	
	25-29	6.30 (1.61-27.75)	0.008	6.09 (1.38-26.85)	**0.02**
	≥30	7.11 (1.48-34.21)	0.01	7.01 (1.28-38.51)	**0.03**
Depth	Deep	1.0 (ref)		1.0 (ref)	
	Superficial	0.51 (0.17-1.57)	0.24	0.68 (0.17-2.70)	0.58
Tumour size (cm)	<10	1.0 (ref)		1.0 (ref)	
	≥10	1.18 (0.39-3.54)	0.78	0.68 (0.05-8.92)	0.77
Volume (cm^3 or ml)	<35.0	1.0 (ref)		1.0 (ref)	
	35.0-149	1.13 (0.32-3.91)	0.85	0.80 (0.19-3.42)	0.76
	150-649	0.79 (0.19-3.28)	0.75	0.73 (0.10-5.32)	0.76
	≥650	1.03 (0.24-4.39)	0.97	0.58 (0.03-11.06)	0.72
Pre-operative radiation	No	1.0 (ref)		-	-
	Yes	0.70 (0.25-1.95)	0.50		
Localisation	Proximal	1.0 (ref)		-	-
	Distal	1.95 (0.73-5.20)	0.18		

[a] No multivariate analysis was performed for the lower extremity since there was no significant difference between free and pedicle flaps in univariate analyses

[b] Upper extremity multivariate model included variables that may affect post-operative complication rates

To determine if free or pedicled flaps were superior in particular "high risk" clinical scenarios we compared their respective complication rates in patients who had large tumours, pre-operative radiation, tumours of the distal extremity or additional bone or vascular resections requiring reconstructive procedures. In the upper extremity free flap reconstructions distal to the elbow had higher complication rates (58% vs 21%, p=0.03) but this was not significant on multivariate analysis (OR 0.13 95% CI 0.01-1.58, p=0.11, Table 5).

Pre- and post-operative functional scores were available for more than half of patients included in this study (TESS: 140 patients (53%), MSTS87: 134 patients (54%), MSTS93: 144 patients (55%)). The difference between the mean pre-operative and post-operative functional scores are outlined in Table 6, where positive scores indicate improved

TABLE 5

Risk factors for complications stratified for flap type and tumour location

Factor		Lower limb, n=181 (68.1%)			Upper limb, n=85 (31.9%)		
		Free n=45 (24.86%)	Pedicled n=136 (75.14%)	p-value	Free n=26 (30.59%)	Pedicled n=59 (69.41%)	p-value
Tumour size (cm)	<10	10 (32.3)	31 (36.6)	0.73	6 (42.9)	10 (20.4)	0.10
	≥10	6 (50.0)	21 (43.7)	0.70	5 (41.7)	1 (11.1)	0.15
Pre-operative radiotherapy	No	2 (28.6)	10 (27.8)	0.97	3 (60.0)	5 (23.8)	0.13
	Yes	14 (36.8)	42 (42.0)	0.58	8 (38.1)	6 (15.8)	0.06
Localisation	Proximal	9 (52.9)	33 (36.3)	0.20	4 (28.6)	6 (17.1)	0.38
	Distal	7 (25.0)	19 (42.2)	0.14	7 (58.3)	5 (20.8)	**0.03***
Additional reconstruction	Yes	12 (54.6)	22 (45.8)	0.50	1 (50.0)	4 (57.1)	0.86
	No	7 (53.9)	7 (30.4)	0.17	1 patient	-	-

*Univariate OR(95%CI)= 0.19 (0.04-0.85), multivariate (adjusted for age, smoker, BMI, stage) OR(95%CI)= 0.13 (0.01-1.58); p=0.11

function, whereas negative scores signify deterioration. There was no significant difference between functional outcomes for patients with free or pedicled flaps in either upper or lower limb reconstructions. Patients with upper limb ESTS who experienced complications were found to have significantly worse function based on MSTS 93 scores compared to those without complications (-8.5 ±10.4 compared to 1.6 ±11.5, p=0.02).

TABLE 6

Differences between the mean pre-and post-operative functional scores, stratified for flap type and complications

		Lower limb; Mean Difference* (SD)			Upper limb; Mean Difference* (SD)		
		TESS	MSTS87	MSTS93	TESS	MSTS87	MSTS93
Flap type	Free	-3.6 (26.2)	-1.6 (5.8)	-2.9 (20.5)	5.5 (17.4)	-1.5 (5.3)	-3.3 (13.8)
	Pedicled	1.8 (15.2)	-0.2 (4.1)	0.6 (14.0)	-0.3 (9.4)	-0.1 (4.1)	0.6 (11.1)
p-value		0.41	0.56	0.12	0.48	0.46	0.84
Complications	No	2.0 (18.6)	-0.7 (4.7)	0.6 (14.8)	2.7 (11.5)	-0.06 (4.3)	1.6 (11.5)
	Yes	-2.6 (18.7)	-0.5 (4.5)	-2.0 (18.1)	-3.7 (14.6)	-2.5 (4.6)	-8.5 (10.4)
p-value		0.21	0.65	0.92	0.81	0.08	**0.02**

*Mean difference is the difference between the mean pre- and post-operative functional scores
Functional results were collected for: TESS: n=140 patients (53%); MSTS87: n=143 patients (54%); MSTS93: n=144 patients (55%). Missing data were excluded from analyses

Discussion

This is, to our knowledge, the largest and most comprehensive study comparing the complications and functional outcomes for patients with ESTS who underwent free or pedicled flap reconstructions. This study confirms that ESTS resection is associated with high complication rates, which is consistent with previous reports and reflects the complexity of limb salvage surgery and frequent use of adjuvant treatments, especially pre-operative radiation.[9,11,16-18] As soft tissue reconstruction is a major component of these procedures, the type of reconstruction performed might be expected to strongly influence post-operative morbidity and function. The results of this study, however, demonstrate that this is not the case as the type of flap used was not an independent predictor of complications in patients with either upper or lower extremity reconstructions. In addition free and pedicled flaps were associated with similar post-operative functional outcomes.

Soft tissue reconstruction following resection of ESTS aims to maximise functional outcomes while minimizing the associated perioperative morbidity. A thorough understanding of the risks and benefits of the proposed reconstructive technique is therefore essential to the informed consent process. This study quantifies the relative complication and functional outcome profiles of free and pedicled flaps in ESTS reconstruction and makes an important contribution to evidence-based decision making in these complex oncological cases.

In this series free flaps were more commonly selected for upper limb reconstructions when tumours were large and deep, which is consistent with the relative absence of large pedicled flaps in this region. In the lower limb however, there was no association between mean tumour size and the use of free or pedicled flaps, which is in line with our clinical experience. For example, in the proximal lower extremity there are a number of large pedicled flap options that can be utilized to reconstruct large soft tissue defects, whereas in the distal lower limb, there are very few reliable pedicled options; hence, free flaps are more frequently required even when tumours are small. This was confirmed by the significant increase in distal leg tumours that required free flap reconstruction.

In the lower limb group, pedicled flaps were associated with a slightly higher risk of complications but this did not reach significance. Conversely in upper limb patients, free flaps were more commonly associated with complications on univariate testing, although this association was not found to be significant on multivariate regression analysis. Upper limb free flap patients had higher mean BMI (Table 1), which probably

accounted for their increased complication rate as increasing BMI was identified as the only significantly independent predictor of complications in the study (Table 4). Obesity has been well recognized as an important risk factor for wound healing complications following complex reconstruction in many studies, including patients with ESTS.[19–23]

In keeping with reports from earlier patient cohorts at our centre, overall post-operative function following free or pedicled flap reconstruction was well preserved with relatively small differences between pre- and post-operative functional scores.[24] Flap choice did not significantly affect functional outcomes in our series. Patients who experienced complications exhibited lower post-operative functional scores, although this difference was only significant for upper extremity patients as measured by MSTS 93 scores ($p=0.02$, Table 6). However, the three functional scores used in this study only consider the site of tumour ablation while flap reconstructions may also result in some degree of impairment at the donor sites, which was not evaluated in this study.

Although this study demonstrates that there is no significant difference between the post-operative complication rates for ESTS patients following free or pedicled flaps, these data are from a high volume centre with a specialist microsurgical practice and the findings must be interpreted accordingly. Institutions with lower volumes may experience higher rates of complications with more complex free flap reconstructions. Although in most patients the choice of flap is determined by the site and size of the defect and the availability of local tissues, in some cases there are other variables that must be considered in the decision making process. For instance, at our institution pre-operative radiation therapy is used frequently so we have considerable experience performing free flap reconstructions 4–6 weeks after completion of radiation. This influences our reconstructive strategy as free flaps may be preferable when adjacent pedicled flaps are located within the field of pre-operative radiation.[25,26] Achieving equivalent results in free and pedicled flap reconstructions is likely to rely heavily on clinical experience and prudent patient selection. It is therefore essential that plastic and orthopaedic oncology surgeons are proficient in all reconstructive options so that the most suitable flap can be selected for each patient.

Free flaps and pedicled flaps were considered collectively in this study so we could not determine if particular types of flaps such as fasciocutaneous or muscle flaps were associated with higher complications rates. As the numbers of individual flaps were small, sub analyses would be underpowered to identify independent associations with complications. This study only included surgical complications as we have previously reported that medical peri-operative complications are rare in this patient population.[23]

However we acknowledge that in certain patients with known medical comorbidities, more complex reconstructive procedures involving extended operating times may be associated with higher complication rates.

Conclusion

In conclusion, this study demonstrates that post-operative complications and functional outcomes associated with either free and or pedicled flaps are equivalent following resection of ESTS. Selecting the most suitable reconstructive option for each individual patient is paramount to achieving good functional outcomes while minimizing post-operative morbidity.

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CHAPTER 7

English summary
Nederlandse samenvatting

English summary

Soft tissue sarcomas (STS) are rare malignant tumours of the soft tissues that account for approximately 1% of the malignancies in adults and mostly arise in the extremities.[1,2] The mainstay of treatment for the majority of patients with STS is wide surgical resection, often necessitating amputation of the affected limb in the past. However, modern treatment including surgery with or without radiotherapy allows limb-preservation in 80-90% of the patients. In many cases this would not be possible without the addition of soft tissue reconstruction.[3–6] Reconstructive surgery plays an important role in extensive STS resections as it achieves wound closure and coverage or reconstruction of critical structures such as bone, nerve, muscle or vessels.[7–11] These however are complex procedures and advances in radiotherapy and chemotherapy protocols combined with higher expectations for limb preservation has led to increased reconstructive challenges. This results in increased operative time with possible extension of post-operative hospital stay, prolonged recovery and rehabilitation. Limb-preserving procedures have shown to improve functional outcomes without increasing the risk for a local recurrence, however it is not yet clear what the effect is of free and pedicled flap reconstructions on post-operative complication rates.[12–15]

In this thesis we aimed to evaluate the role of flap reconstructions on post-operative complications in the surgical treatment of STS. Additionally, predictors for complications were explored in order to identify patients at risk for adverse events in these complex surgical procedures.

Firstly, a systematic search for all published literature describing risk factors for complications in the surgical treatment of extremity soft tissue sarcomas (ESTS) was performed, presented in **Chapter 2**. This systematic review shows that the number of studies published on this topic is limited and the quality of the data is generally fairly poor. The number of patients included is often limited and all but one study were retrospective in nature. However, from the thirteen included papers it can be concluded that the overall complication rate ranges from 25 to 36 percent and the re-operation rate is approximately 14 percent. Individual studies reported that age, obesity, smoking, diabetes, tumour size, tumour site and pre-operative radiotherapy were associated with adverse outcomes. Tumours of the lower limb, diabetes and radiation were identified as important predictors of wound complications in meta-analysis. The impact of flap reconstruction on post-operative complications was inconclusive with both positive and negative effects reported. Many studies, however, did not include flap reconstruction in

their multivariate analyses, which makes conclusions difficult. In addition, there was heterogeneity between studies with regard to inclusion and definition of complications which hampered accurate pooling of the study results. Therefore, there is a need for more uniform reporting of complications and their associated risk factors to make individualized risk assessment of STS patients more accurate in the future.

Chapter 3 describes the value of the American College of Surgeons National Surgical Improvement Program (ACS-NSQIP) surgical risk calculator in patients requiring STS resection followed by a flap reconstruction. The calculator is created from a large database and used for identification of patients at risk for post-operative complications in a wide range of surgical procedures.[16–18] It is an online and open access tool for both patients and surgeons to predict the risk for 11 post-operative complications, based on patient-specific and treatment-specific variables for 1500 different surgical procedures. To study the applicability of the ACS NSQIP surgical risk calculator in this patient population, the predicted complication rates of the calculator were compared with the observed rates of complications in 265 patients requiring flap reconstruction following STS resection. Although a personalized risk calculator would be a valuable tool for pre-operative consultations of STS patients, the results of this study show that the ACS NSQIP risk calculator underestimates complication rates and does not correctly identify patients at risk for complications following flap reconstructions. The discrepancy between predicted and observed complication rates may be due to heterogeneity of the study population and the limited procedure codes that can be entered in the ACS NSQIP calculator. Furthermore, the omission of certain important factors in the calculator, such as tumour size, tumour site, the complexity of the procedure and adjuvant therapies (chemotherapy or radiotherapy) may be a reason for the observed discrepancy.

Therefore, factors contributing to complications in patients requiring flap reconstruction following STS excision were studied in more detail and are described in **Chapter 4, 5 and 6**. The first aim was to identify independent risk factors for complications in this specific patient group, which are described in **Chapter 4**. The results of this study show that a history of cerebrovascular events or cardiac disease, tumour grade and the need for additional reconstructive procedures (vascular, bone, muscle or abdominal repair) were important independent predictors of complications in this patient group. In addition to this, possible synergistic interactions between risk factors were explored to aid in the development of a more individualised complication-risk assessment. Synergistic interaction means that the effect of two risk factors taken together is greater than the sum of their individual effect, indicating that they amplify each other in the development of complications. This synergistic interaction was observed in obese patients with either

a large tumour or high tumour grade and also in patients with comorbidities and large tumours. These results show that the development of complications is multifactorial and highlights the importance of considering the combined effect of risk factors in the pre-operative assessment of patients. Moreover, these results support the hypotheses in **Chapter 3** that the omission of many tumour- and treatment related factors in the ACS NSQIP risk calculator may have compromised its efficacy to accurately predict complications following flap reconstruction of STS defects. Finally, the results show that some predictors of complications, such as radiotherapy and tumour location in the lower extremity, that have been previously identified in STS patients where no flaps were used, are not correlated with complications in STS defects closed with free or pedicled flap reconstructions. Flaps transfer well-vascularized tissue, unaffected by the tumour or previous treatments and facilitate tension free closure, possibly mitigating the effect of previously identified predictors of complications in patients treated with primary closure.

To explore if there are indeed differences in complications and predictors of complications between patients with and without flap reconstructions, 897 patients with ESTS were studied and described in **Chapter 5**. Complication rates and risk factors for complications were compared between 266 patients undergoing flap reconstruction and 631 patients with primary wound closure after ESTS resection. The results of this study showed that flap reconstructions were not associated with significantly increased post-operative complication rates in multivariate analyses. Another interesting finding was the difference in observed predictors of complications between patient groups. Tumour location at the lower extremity and pre-operative radiation, which are a well-known risk factors for complications, where the strongest predictors for complications in the study group as a whole as well as in the primary closure group, but not in the flap reconstruction group. Conversely, important predictors of complications in the flap reconstruction group such as comorbidities, increased BMI and the presence of metastatic disease were not predictors in patients with primary wound closure. This suggests that flap reconstructions may mitigate the negative effect on wound healing of some tumour-and treatment-related risk factors, but may be associated with increased complications in obese patients or those with systemic disease.

Finally, in **Chapter 6** the outcomes of 71 free and 195 pedicled flap reconstructions following ESTS resection are described. Complications and functional results were compared between study groups in order to determine if flap selection influenced outcomes. In the upper extremity free flaps were associated with more complications in univariate analysis, however, high BMI was the only independent predictor of

complications in multivariate analyses. In the lower extremity, there was no difference in complication rates between free and pedicled flap groups on univariate analysis. There was no difference in functional results between the flap groups. Although free flaps are more complex procedures they were not associated with increased complications in this series. These findings are, however, likely to be dependent on clinical experience and prudent flap selection and confirm the importance of treatment in a specialised centre that is familiar with all reconstructive options to assure accurate selection and provision of the most suitable reconstructive option in each patient.

Conclusions

The results of the five studies described in this thesis confirm that resection of soft tissue sarcomas (STS) is associated with high rates of complications, reflecting the complexity of limb-preserving treatment in these patients. This thesis identifies deficiencies in our understanding of the causes of post-operative complications and our ability to predict them. Our studies show that multiple patient and treatment factors contribute to post-operative complications in STS patients. In the evaluation and pre-operative counselling of patients with STS it is therefore essential to identify specific risk factors for complications to provide accurate information on the risks and benefits of a proposed treatment. The combined effect of multiple patient, tumour and treatment factors should be considered, as synergistic interaction between variables can further increase the risk of complications. Overall, patients requiring flap reconstruction following STS resection are not at higher risk for complications. Selected patients with distal lower extremity tumours or those requiring pre-operative radiotherapy might benefit from reconstructive surgery, as the importation of well vascularised tissue may aid wound healing. In contrast, patients with comorbidities, increased BMI or advanced disease seem to be at higher risk for post-operative morbidity after extensive reconstructions. The results of this thesis enhance our knowledge of complication rates and contributing factors in patients undergoing STS resection and will contribute to improved pre-operative risk assessment and personalised care in the future.

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Nederlandse samenvatting - Dutch summary

Sarcomen van de weke delen (soft tissue sarcomas; STS) zijn zeldzame kwaadaardige tumoren, uitgaande van de weke delen (steun- en tussenweefsels in het lichaam zoals huid, bindweefsel, vet, spieren, zenuwen, bloedvaten en lymfevaten). Ze vormen ongeveer één procent van alle nieuwe gevallen van kanker bij volwassenen per jaar. Een STS kan op allerlei plaatsen in het lichaam ontstaan, maar de meerderheid van de tumoren komt voor op de ledematen. Het is onbekend hoe sarcomen precies ontstaan. Een STS begint vaak als een pijnloze zwelling en geeft weinig of geen klachten, waardoor de tumor vaak pas laat wordt opgemerkt. Alarmsymptomen zijn (snelle) groei van een al eerder bestaande of nieuwe zwelling, een diameter van meer dan 5 centimeter en tumoren die doorgroeien tot in de spierfascie.

Sarcomen van de weke delen vertonen vaak een lokaal agressieve groeiwijze met een grote neiging tot hematogene metastasering. Metastasering naar de lymfklieren komt zelden voor. In de meeste gevallen kan een STS operatief verwijderd worden, waarbij er ook een deel gezond weefsel rondom de tumor meegenomen wordt om de tumor volledig te verwijderen en een recidief te voorkomen. Amputatie van een arm- of been was in het verleden een gebruikelijke behandeling van een STS. Verbetering van de beeldvorming en behandelstrategieën hebben er echter in de afgelopen jaren toe geleid dat 80 tot 90 procent van de patiënten tegenwoordig ledemaat-sparend behandeld kan worden. Neoadjuvante therapieën zoals preoperatieve radiotherapie en in sommige gevallen chemotherapie kunnen de tumor verkleinen om zo resectie te bewerkstelligen. Daarnaast kan postoperatieve radiotherapie geïndiceerd zijn om de kans op een recidief te verkleinen. Pre- en postoperatieve radiotherapie kunnen echter wel tot een vertraagde wondgenezing leiden.

Door de genoemde verbeterde behandelstrategieën zijn steeds grotere tumoren operatief te verwijderen, met als gevolg grotere operatiewonden. De reconstructieve chirurgie speelt een cruciale rol om tijdens complexe operaties belangrijke structuren zoals zenuwen, bloedvaten, spieren en bot te reconstrueren of met vitaal weefsel te bedekken. Daarnaast zijn gesteelde en vrije reconstructieve lappen in veel van deze gevallen noodzakelijk om de wond te kunnen sluiten. Dit zijn echter technisch ingewikkelde procedures, die gepaard kunnen gaan met een langere operatieduur en potentieel een langere opnameduur en/of postoperatief herstel. Ledemaat-sparende procedures hebben aangetoond bij te dragen aan een beter functioneel herstel dan een amputatie, zonder het risico op een tumorrecidief te vergroten. Over het effect van

reconstructieve chirurgie op het ontwikkelen van postoperatieve complicaties is echter nog onvoldoende bekend.

In dit proefschrift wordt de invloed van de reconstructieve chirurgie op postoperatieve complicaties in de behandeling van patiënten met STS geëvalueerd. Tevens worden risicofactoren voor complicaties in dezelfde patiëntenpopulatie geanalyseerd om hiermee patiënten met een hoog risico op complicaties te identificeren en operatie-uitkomsten mogelijk te verbeteren.

In een systematische review worden de risicofactoren voor complicaties na chirurgische behandeling van STS in de ledematen besproken, weergegeven in **hoofdstuk 2**. Uit deze review bleek dat het aantal studies en de studiekwaliteit op dit onderzoeksgebied gering was. Het aantal geïncludeerde patiënten was vaak minimaal en alle studies behoudens één hadden een retrospectieve studieopzet. Uit de 13 geïncludeerde studies kan echter wel worden geconcludeerd dat het percentage postoperatieve complicaties tussen de 25 en 36 procent ligt en dat het risico op een re-operatie ongeveer 14 procent is. Uit de verscheidende studies kwam naar voren dat roken, leeftijd, obesitas, diabetes, tumorgrootte, tumorlocatie en preoperatieve radiotherapie van invloed zijn op het ontwikkelen van complicaties na resectie van een STS. Meta-analyse van deze data toonde dat tumoren van de onderste ledematen, diabetes en preoperatieve radiotherapie de voornaamste risicofactoren zijn voor postoperatieve complicaties. De resultaten met betrekking tot de invloed van reconstructieve chirurgie op het ontwikkelen van complicaties waren niet conclusief, waarbij zowel positieve- alsook negatieve invloed op postoperatieve complicaties werd gerapporteerd. De meerderheid van de studies includeerde de invloed van reconstructies niet in multivariate analyse, waardoor er geen overtuigende conclusies konden worden getrokken. Tevens bestond er een grote heterogeniteit tussen de studies op het gebied van inclusie en de definitie van complicaties waardoor adequate analyse van de resultaten belemmerd werd. Meer uniforme rapportage van complicaties en de geassocieerde risicofactoren is daarom essentieel om de uitkomsten van verschillende onderzoeken te kunnen vergelijken en om beter te kunnen inschatten welke patiënten met STS een hoger risico hebben op het ontwikkelen van postoperatieve complicaties.

Hoofdstuk 3 beschrijft de validiteit van de American College of Surgeons National Surgical Improvement Program (ACS NSQIP) surgical risk calculator bij patiënten met een lapreconstructie na resectie van een STS. Deze online calculator is een hulpmiddel om preoperatief een inschatting te maken voor het ontwikkelen van eventuele postoperatieve complicaties op basis van de voorgenomen ingreep en 21 patiëntfactoren

(zoals bijvoorbeeld leeftijd en gewicht). Hiermee wordt een hulpmiddel geboden om de arts en patiënt adequate voorlichting te geven ter voorbereiding op een operatie. Om de validiteit van de ACS NSQIP surgical risk calculator te onderzoeken werden de complicaties voorspeld door de ACS NSQIP calculator vergeleken met de daadwerkelijk opgetreden complicaties van 265 patiënten met een lapreconstructie na een STS-resectie. De risk calculator werd gevalideerd door middel van drie verschillende statistische testen, die ook gebruikt zijn voor de totstandkoming van de originele ACS NSQIP surgical risk calculator. Hoewel een patiënt-specifieke tool om het complicatierisico te kunnen voorspellen een waardevolle toevoeging zou kunnen zijn in de preoperatieve consultvoering van patiënten met STS, toont deze studie dat de ACS NSQIP surgical risk calculator het complicatierisico onderschat en niet accuraat voorspelt welke patiënten een hoger risico hebben op het ontwikkelen van complicaties. De discrepantie tussen het voorspelde en daadwerkelijk opgetreden complicatierisico kan het gevolg zijn van de heterogeniteit van de studiepopulatie en het gelimiteerd aantal procedurecodes die ingevoerd konden worden in de ACS NSQIP calculator. Daarnaast zou het ontbreken van belangrijke tumor gerelateerde factoren, zoals tumorgrootte en tumorlocatie, de complexiteitsgraad van de procedure en adjuvante therapieën, zoals radiotherapie en chemotherapie, van invloed kunnen zijn op de geobserveerde discrepantie.

Naar aanleiding van de uitkomsten in de voorgaande hoofdstukken zijn de factoren van invloed op het ontwikkelend van complicaties bij patiënten met een lapreconstructie na STS-resectie nader onderzocht in de **hoofstukken 4, 5 en 6**. Onafhankelijke risicofactoren voor complicaties werden in deze studiegroep onderzocht, die zijn beschreven in **hoofdstuk 4**. De resultaten van deze studie laten zien dat een cerebrovasculaire of cardiale voorgeschiedenis, de tumorgraad en de noodzaak voor aanvullende reconstructieve chirurgische procedures (reconstructie van bloedvaten, bot, spier of abdomen) belangrijke onafhankelijke risicofactoren voor complicaties zijn in deze patiëntengroep. Tevens werden synergetische interacties tussen risicofactoren geëxploreerd. Met synergetische interactie wordt bedoeld dat het effect van twee risicofactoren samen groter is dan de som van beide afzonderlijke risicofactoren doordat ze elkaar versterken. Deze synergetische interactie werd gezien bij obese patiënten met een grote tumor of hoge tumorgraad alsook bij patiënten met één of meerdere comorbiditeiten en grote tumoren. Deze resultaten benadrukken de multifactoriële aard van complicaties en demonstreren dat het belangrijk is om tijdens de preoperatieve beoordeling van patiënten het onderlinge versterkende effect van verschillende risicofactoren in acht te nemen en dit te bespreken met de patiënt. Deze bevindingen ondersteunen bovendien de hypothese in **hoofdstuk 3** dat de afwezigheid van bepaalde

tumor- en behandeling gerelateerde factoren in de ACS NSQIP surgical risk calculator een mogelijke verklaring is voor de inaccurate predictie van het complicatierisico van de calculator bij patiënten met reconstructieve chirurgie na STS-resectie. Tenslotte tonen de resultaten dat bepaalde risicofactoren die in eerder onderzoek zijn geassocieerd met complicaties bij patiënten met STS-resectie zonder lapreconstructie, zoals radiotherapie en tumor lokalisatie in de onderste ledematen, niet geassocieerd zijn met complicaties wanneer een operatiewond wordt gesloten met een vrije of gesteelde lap. Lapreconstructies bewerkstelligen een tractievrije wondsluiting met daarbij goed gevasculariseerd weefsel, onaangetast door de tumor of voorgaande behandelingen zoals radiotherapie, waardoor het effect van eerder geïdentificeerde risicofactoren voor complicaties bij patiënten met primaire wondsluiting mogelijk verminderd wordt.

In **hoofdstuk 5** werd onderzocht of er inderdaad verschillen in complicaties en in risicofactoren voor complicaties zijn tussen patiënten met en zonder lapreconstructie na resectie van een STS in de ledematen (ESTS). In deze studie werden de complicaties en onafhankelijke risicofactoren voor complicaties van 266 patiënten met een lapreconstructie na ESTS-resectie vergeleken met 631 patiënten waarbij de wond primair gesloten was. Patiënten in de groep met lapreconstructies waren significant ouder, hadden vaker een tumor in het distale deel van de ledematen en hadden vaker een vergevorderde ziekte (stadium III of IV) waarbij radiotherapie of chemotherapie frequenter noodzakelijk was. Multivariate analyse toonde dat patiënten met een lapreconstructie na ESTS-resectie geen significant verhoogd risico hadden op het ontwikkelen van complicaties. Een andere interessante bevinding was het verschil in risicofactoren voor complicaties tussen beide studiegroepen. Tumorlocatie in de onderste ledematen en preoperatieve radiotherapie, beide bekende voorspellers van complicaties, waren het sterkst gecorreleerd met complicaties in de totale studiegroep alsook in de groep met primaire wondsluiting, echter niet bij de patiënten met reconstructieve chirurgie na ESTS-resectie. De aanwezigheid van comorbiditeiten, een metastase of een hoog BMI vormen juist belangrijke risicofactoren in de reconstructieve groep, die geen voorspellers van complicaties in de groep met primaire wondsluiting zijn. Dit suggereert dat lapreconstructies na ESTS-resectie het negatieve effect van sommige tumor- en behandeling gerelateerde risicofactoren zouden kunnen tegengaan maar geassocieerd zijn met meer complicaties bij mensen met obesitas, comorbiditeiten of een gemetastaseerde ziekte.

Tenslotte zijn de postoperatieve uitkomsten van vrije en gesteelde lappen na STS-resectie beschreven in **hoofdstuk 6**. De complicaties en functionele resultaten van 71 patiënten met vrije lappen en 195 patiënten met gesteelde lappen werden vergeleken

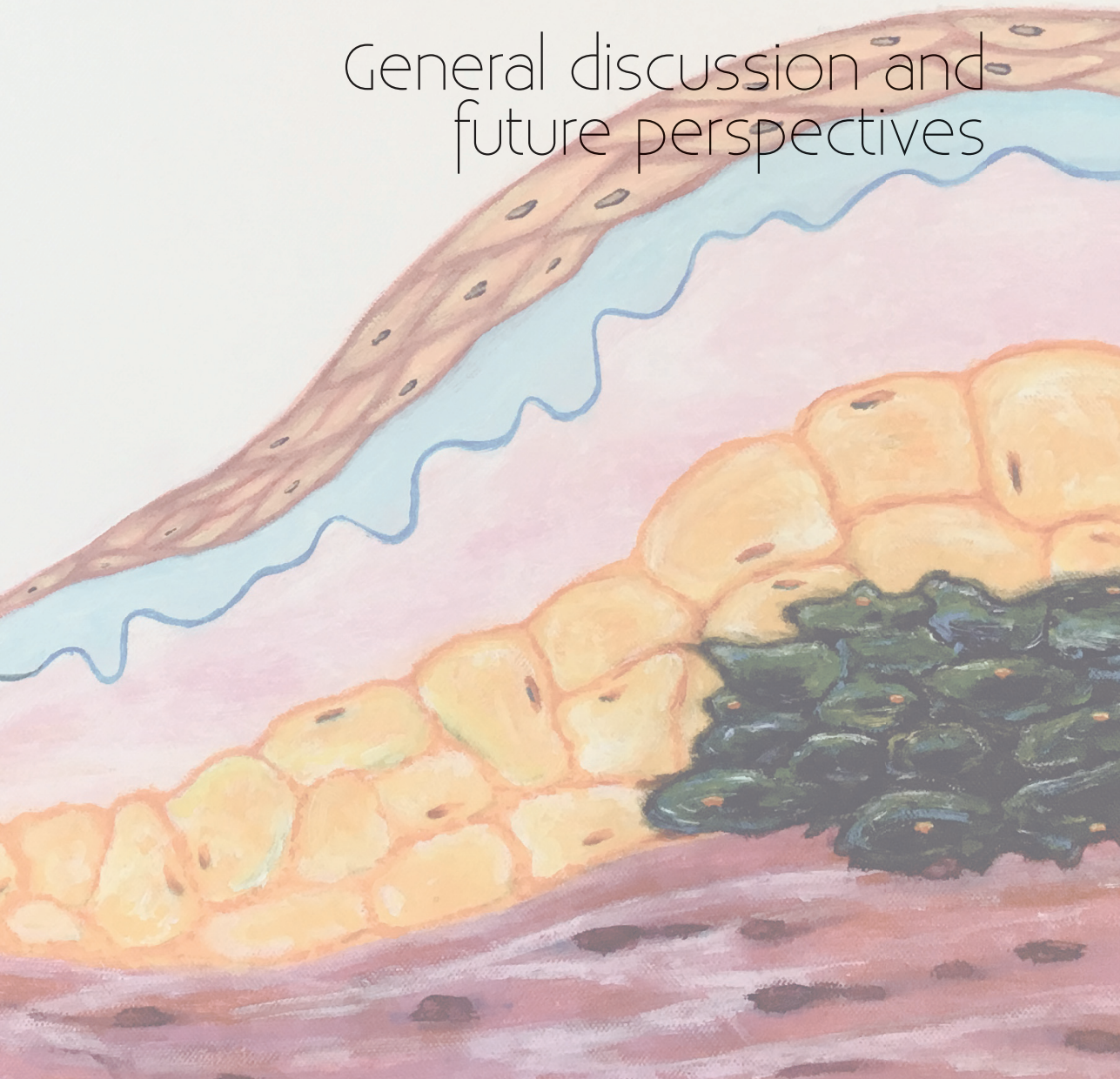
om te achterhalen of lap selectie invloed heeft op de postoperatieve uitkomsten. In de bovenste ledematen waren vrije lappen geassocieerd met meer complicaties in univariate analyse, terwijl een hoge BMI de enige onafhankelijke prognostische factor was die significant bleef in multivariate analyse. In de onderste ledematen was er geen verschil in complicaties in univariate analyse tussen beide reconstructieve methoden. De functionele resultaten waren eveneens overeenkomstig tussen vrije en gesteelde lappen. Hoewel vrije lappen complexere reconstructies zijn, werd dit niet geassocieerd met meer complicaties in deze patiëntengroep. Echter, dit is waarschijnlijk te verklaren met de ruime chirurgische expertise en adequate lapselectie in een gespecialiseerd sarcoomcentrum. Deze bevindingen ondersteunen het belang van behandeling in een gespecialiseerd multidisciplinair centrum om een patiënt de meest geschikte reconstructieve opties te bieden.

Conclusie

De resultaten van de vijf studies beschreven in dit proefschrift bevestigen dat resectie van STS gepaard gaat met een hoog percentage complicaties, hetgeen de complexiteit van de ledemaat-sparende behandeling van deze patiënten weerspiegelt. Dit proefschrift toont de tekortkomingen in de kennis van de oorzaken van postoperatieve complicaties en ons beperkte vermogen om deze te kunnen voorspellen. De studies tonen dat verscheidene patiënt-,tumor- en behandeling gerelateerde factoren bijdragen aan het ontwikkelen van postoperatieve complicaties bij patiënten met een STS. In de preoperatieve beoordeling en evaluatie van deze patiënten is het daarom essentieel om risicofactoren voor complicaties te identificeren om patiënten goed te kunnen informeren over de voor- en nadelen van de voorgenomen ingreep. Bij aanwezigheid van verscheidene risicofactoren moet bovendien rekening gehouden worden met de synergetische interactie tussen verschillende patiënt-, tumor- en behandeling gerelateerde risicofactoren. Uit het proefschrift bleek dat patiënten met een lapreconstructie na STS-resectie geen verhoogd risico op complicaties hebben vergeleken met patiënten waarbij de wond primair gesloten wordt. Patiënten met een tumor in de onderste ledematen of bij wie radiotherapie noodzakelijk is kunnen bovendien zelfs voordeel hebben van een vrije of gesteelde lap, vanwege het vermeende positieve effect op wondgenezing bij deze patiënten. Patiënten met de aanwezigheid van comorbiditeiten, gemetastaseerde ziekte of verhoogd BMI lijken echter een groter risico te hebben op complicaties na STS-resectie gevolgd door een lapreconstructie. De resultaten van dit proefschrift dragen bij aan de kennis ten aanzien van complicaties en de risicofactoren van complicaties bij patiënten na STS-resectie. Met deze kennis kan de preoperatieve risico-inschatting op complicaties worden verbeterd om zo de zorg voor patiënten met STS te optimaliseren.

CHAPTER 8

General discussion and future perspectives



Future perspectives

Treatment of soft tissue sarcoma (STS) patients has shifted towards a coordinated multidisciplinary treatment in large sarcoma centres in the past years.[1,2] Although historically a limb amputation was standard of care, it is currently rarely indicated due to the proven effectiveness of pre- or post-operative radiation therapy in the limb-salvaging treatment of ESTS.[3–6] Moreover, 70-80% of the primarily irresectable ESTS become resectable after a neo-adjuvant treatment with hyperthermic isolated limb perfusions (HILP) with TNFα and mephalan.[7–9] Therefore, most amputations are currently solely performed after primary limb-salvage failure, due to short or long-term treatment-related morbidity or local recurrent disease. Most STS-types are not particularly sensitive to chemotherapy and is therefore indicated for only a few sarcomas such as rhabdomyosarcoma, Ewing sarcoma and osteogenic sarcoma. Increasingly effective disease targeting drugs are available for various sarcoma subtypes, such as imatinib for locally advanced and unresectable gastrointestinal stromal tumours (GIST) and uncontrollable dermatofibrosarcoma protuberans (DFSP).[10,11] Although surgery is the cornerstone of STS treatment, the role of other specialities such as pathology, radiology, surgery, radiotherapy, medical oncology, epidemiology, medical genetics as well as nuclear medicine specialists will continue to increase. In this chapter, some aspects of future STS treatment are highlighted.

Diagnosis

Histopathology remains the basis for accurate diagnosis of STS. The treatment and prognosis of STS are highly influenced by the tumour histopathology, since it reflects the aggressiveness and extent of differentiation or dedifferentiation of the tumour. Currently histological type, grade, presence of necrosis, presence of mitotic rate and the margin status are the cornerstones of pathologic staging of STS.[12–14] However, despite the recognition and better understanding of different STS-types, treatment guidelines still mainly provide general treatment recommendations for nearly all STS-subtypes, and subtype-specific treatment protocols exist for only a few entities. Also, in some tumour types variable morphologic regions coexist in one tumour.

Genomic revolutions in cancer give further insight into the molecular aspects of the different STS-subtypes.[15,16] With this, the development of new targeted therapeutics directed against specific molecular pathways has allowed an essential improvement in cancer treatment. For STS however, there is a lack of innovative approaches due to

the high degree of heterogeneity of this tumour type, the limited knowledge of the molecular drivers of tumour development and progression, and the low incidence. Therefore, more studies are needed in the future to better understand tumour biology of different STS types, to derive new prognostic and diagnostic markers and to develop new targeted therapeutics for different STS subtypes.[17–19] Promising new therapeutic agents such as target– and immunotherapy that attack specific mechanisms of STS cells have already been reported.[20–23] This may aid in STS-subtype specific treatment that is more effective and less toxic. However, optimal strategies for these therapies in STS are yet to be determined.

Imaging techniques

Diagnosing STS accurately is often challenging and therefore the complimentary use of both pathology and imaging techniques is required during this process. Imaging is not only important in the diagnosis, staging and treatment planning, but provides crucial information for treatment evaluation and follow-up as well. Computerized tomography (CT) and magnetic resonance imaging (MRI) are both reliable options. CT is generally preferred for imaging of chest, abdomen and pelvis STS and MRI is usually preferred for evaluation of extremity and head and neck STS. These techniques continue to evolve with three-dimensional (3D) imaging techniques further facilitating pre-operative treatment planning and diffusion-weighted MRI potentially aiding in the assessment of treatment response.[24–26]

Imaging with Positron Emission Tomography (PET) scan with 18F-fluorodeoxyglucose (FDG) can visualise the metabolic activity of sarcoma. Generally, high grade sarcoma (e.g. Ewing or rhabdomyosarcoma) show high FDG uptake, whereas low grade sarcoma (e.g. liposarcoma) show low uptake. Although the use of FDG-PET in the diagnosis of sarcoma is still being defined, new techniques combining PET with a high-resolution anatomical imaging modality such as CT or MRI provide a very good insight into the local tumour growth and tumour heterogeneity, the presence of metastasis and therapy evaluation, which will likely optimise diagnostics and treatment in the future.[27–30] Moreover, recent literature has shown that PET-CT may play an important role in guidance of biopsies to get a representative sample of the most aggressive parts of the tumour.[28] Additionally, FDG-PET/CT could be used during follow-up after treatment for early detection of local recurrence or metastasis, especially in high grade sarcoma.[31] However, it is questionable if these new and often expensive new techniques are cost-effective.

Radiation techniques

Pre- or post-operative external beam radiotherapy (EBRT) has been widely used in the treatment of STS to gain better local tumour control. Pre-operative radiotherapy is normally given in 25 fractions of 2 Gy, with a total dose of 50Gy whereas post-operative radiotherapy results in a total dose of 60-70 Gy (30-35 fractions of 2 Gy). The timing of RT in primary ESTS is still debated since no significant differences in local control and survival between patients treated with either pre-operative or post-operative EBRT in addition to LSS have been shown to date.[32–35] The use of pre-operative EBRT shows higher acute post-operative complications but has the advantage of smaller radiation fields and lower total radiation doses, resulting in better long term functional outcomes than post-operative EBRT due to less fibrosis, joint stiffness and edema.[32,36–39] Therefore, several studies are currently addressing the potential to reduce treatment volumes in order to reduce complications without decreasing oncologic outcomes (DOREMY-study NCT02106312 and CRUK-VORTEX study, NCT00423618). The results from these trials are awaited.

Various other radiation techniques have been studied to reduce toxicities and improve functional outcome without compromising local control. The addition of intraoperative electron radiation therapy (IOERT)[40–42] or brachytherapy[43,44] offers the surgeon direct visualization of the surgical bed with shorter treatment duration and better sparing of normal tissue than external beam radiotherapy (EBRT), which may translate to a lower rate of complications. These were promising radiation techniques in the eighties and nineties, but the technology was not widely accepted in the sarcoma community. Other promising techniques are intensity-modulated radiotherapy (IMRT; external-beam radiotherapy that uses photon radiation beams with varying fluences across multiple radiation fields) and hypofractionated EBRT, where the total dose of radiation is divided into large doses per fraction with fewer fractions.[44–47] The next decade will show if these radiation techniques will achieve a definitive place for the treatment of certain anatomical locations.

Surgical treatment

Surgery is the cornerstone of the management of patients with STS. The wider the local excision, the lower the probability of local failure, however larger defects are more prone for delayed wound healing. In addition, some aspects of specific STS-subtypes, such as the local growth pattern, the preferred anatomical location and the need for radiotherapy or chemotherapy may influence the surgical approach. In the future, adequate surgical

resection of STS might be further improved by the support of real-time optical imaging techniques such as molecular fluorescence-guided surgery (MFGS).[48–50] Currently, surgeons depend on visual and tactile information to differentiate between healthy and tumour tissue. However, MFGS can potentially be of added value for more adequate differentiation based on the molecular characteristics of tumour cells. For this purpose, near-infrared (NIR) fluorescence agents can be used that specifically target certain receptors that are overexpressed in STS, or become activated by proteolytic enzymes or changes in pH that are characteristic for tumour cells. Consequently, these techniques have the potential to decrease the amount of resections with positive margins, leading to improved oncologic results. This is especially important in STS surgery were recurrence rates are known to be high.

These techniques, in combination with increased surgical experience over time will hopefully substantially improve oncologic, morbidity and functional outcomes of STS surgery in the future. The above mentioned technologies need to be refined by large collaborative studies to further improve diagnoses, treatment and recovery of patients with STS. However, one thing is clear; multidisciplinary care remains essential in the treatment of patients with STS.

Post-operative complications

There is an increasing need for disease specific calculators to provide individualized pre-operative risk assessment. Increased knowledge of predictors of wound complications enhances our ability to identify patients at risk for developing complications. In addition, improvements in diagnostic and imaging techniques may aid early recognition of STS and reduce the extent of surgical resections and lower post-operative wound complication rates.

The findings of the studies in this thesis show that the development of complications is multifactorial. Moreover, the effects of risk factors on complications in STS patients undergoing flap reconstruction differ considerably from risk factors of patients undergoing primary wound closure, which have been studied more extensively. We found that tumours at the lower extremity and radiotherapy, which are well-known risk factors for complications and were also independent predictors of complications in our primary closure group, did not significantly impact morbidity when using a flap reconstruction. In patients requiring reconstructions however, caution should be taken in patients with a high BMI or comorbidities as these seem to be at higher risk of post-operative morbidities and have synergistic interaction with tumour-related

factors such as tumour grade and tumour size in the development of complications. This highlights the importance of considering risk factors specific to STS patients undergoing flap reconstruction. Future studies specific to this patient group will aid in the understanding of these patients and the development of an individualized pre-operative risk assessment tool. Ideally, in future there will be more accurate and personalized risk assessment including patient, tumour and treatment factors with the ability to combine procedures in cases of complex reconstruction such as the need for vascular, neural or bony reconstruction, while recognizing possible interactions between risk factors. The data of this thesis may provide the basis for this.

In addition, the results of the papers in this thesis only consider risk factors for short term complications. Information on long term sequelae such as functional results, locoregional recurrence and survival rates may also be of significant assistance to these patients in their decision making process. A disease-specific calculator including these factors can improve individualized risk prediction and enhance pre-operative counselling and planning in the future.

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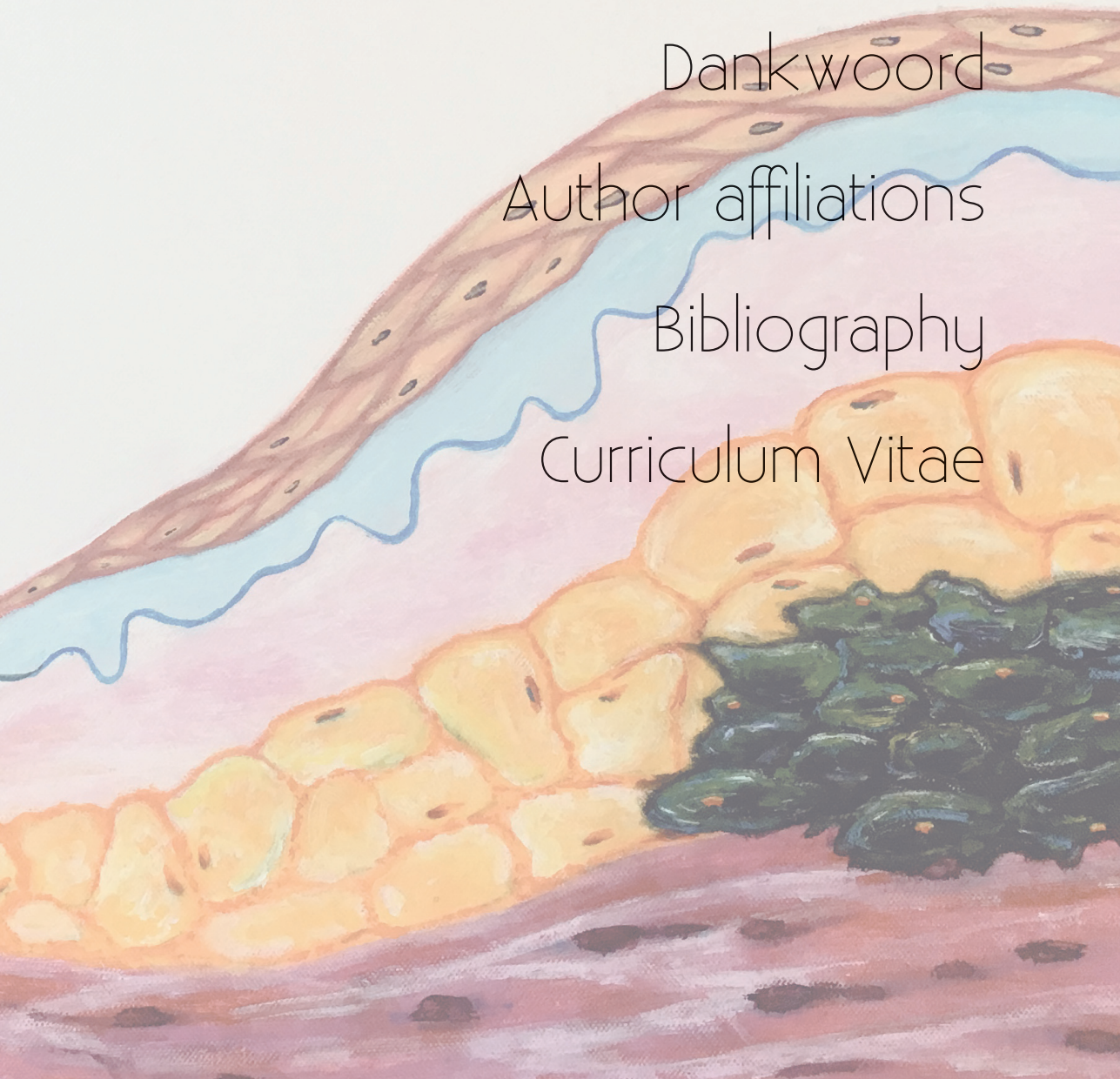
APPENDICES



Dankwoord

Author affiliations

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Dankwoord

Zing

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Curriculum Vitae

Jelena Slump werd geboren op 11 oktober 1988 te Heerenveen, waar ze opgroeide als dochter van Jan en Dineke Slump samen met haar zussen Annelyt en Yanieke. Na het behalen van haar VWO-diploma aan de O.S.G. Sevenwolden, begon ze in 2007 aan haar studie Geneeskunde aan de Rijksuniversiteit van Groningen. Naast haar studie was Jelena actief in diverse commissies en in het bestuur van de Medische Faculteitsvereniging Panacea. Ook heeft ze in die periode verschillende reizen gemaakt en is ze in 2013 voor een coschap Tropengeneeskunde in Rwanda geweest.

Tijdens haar studie werd Jelena's belangstelling gewekt voor de Plastische Chirurgie. In haar laatste studiejaar volgde ze daarom haar semi-arts stages op de afdelingen Plastische Chirurgie en Algemene Chirurgie in het Isala Ziekenhuis te Zwolle.

Na deze stages te hebben afgerond, startte ze in 2015 haar onderzoek bij de afdeling Plastische en Reconstructieve Chirurgie in Toronto General Hospital, Canada. Onder begeleiding van prof. dr. S.O.P. Hofer, prof. dr. H.J. Hoekstra en dr. A.C. O'Neill heeft ze een jaar onderzoek in Toronto gedaan op het gebied van reconstructies in de behandeling van wekedelen sarcomen. Dit onderzoek is de basis geweest voor haar promotie over dit onderwerp.

Bij terugkomst in Nederland heeft Jelena haar onderzoek vervolgd op de afdeling Chirurgische Oncologie van het Universitair Medisch Centrum Groningen (UMCG). Naast haar promotiewerkzaamheden gaf Jelena schilderlessen en was ze actief als zangeres bij "Slump en Bakker niks van" en het koor "Roxie". Eind 2017 is ze in Panama geweest om te werken bij "Floating Doctors". Begin 2018 bood ze haar proefschrift getiteld "The role of reconstructive surgery in the treatment of soft tissue sarcomas" aan ter verkrijging van de doctorsgraad.

Op dit moment is Jelena werkzaam in het Martini ziekenhuis te Groningen als ANIOS op de afdeling Chirurgie en ze zal op 1 december beginnen als ANIOS op de afdeling Plastische Chirurgie in het UMCG.