



## 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 preoperative 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.

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**Keywords:** 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.<sup>1,2</sup> 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.<sup>3–5</sup> This combined approach enables effective oncological ablation while maximizing preservation of function.<sup>4,6,7</sup>

Although the benefits of soft tissue reconstruction are clear, the addition of free or pedicled flaps increases the

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complexity of the surgery, which extends both the operative and recovery times.<sup>4,8,9</sup> Identifying patients who are at high risk for post-operative complications is important in the preoperative assessment. Even in cases where the surgical strategy will not change, accurate and personalized estimation of risk is a critical component of effective preoperative 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.<sup>10–13</sup>

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.<sup>9,14,15</sup> The primary objective of this study was to identify independent predictors of postoperative 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 postoperative surgical and medical complications were recorded and graded according to the Clavien–Dindo classification of surgical complications.<sup>16</sup>

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.<sup>17</sup>

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.<sup>18</sup>

## 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 ( $\pm 18.9$ , range 18–97) and mean BMI of 26.9 ( $\pm 6.6$ , 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.

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  $\geq 10$  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 preoperative radiation. Conversely relatively few patients (6%) had preoperative 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 postoperative 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  $\leq 2$ ; 22.5%), and 20 percent were major complications (Clavien–Dindo grade  $\geq 2$ ). 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

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