



Original Research

High-risk soft tissue sarcomas treated with perioperative chemotherapy: Improving prognostic classification in a randomised clinical trial



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Abstract Background: Patients with extremity and trunk wall soft tissue sarcoma (STS) with high malignancy grade and size >5 cm are at high-risk of death. This risk varies depending also on other patient and tumour features, including histologic subtype. This study investigated whether a prognostic nomogram can improve risk assessment of these patients.

Methods: Data from high-risk STS patients enrolled in a randomised controlled trial investigating different perioperative chemotherapy regimens were analysed. Ten-year probability of overall survival (OS) and incidence of distant metastasis (DM) were computed using the prognostic nomogram Sarcuator (pr-OS and inc-DM, respectively). Tumour response according to RECIST and Choi criteria was also investigated.

Findings: Variation in pr-OS and inc-DM were observed and patients stratified in three prognostic groups. The 10-year OS in the low, intermediate, and high pr-OS categories were 0.42 (95%CI 0.32–0.52), 0.63 (95%CI 0.53–0.72), and 0.78 (95%CI 0.68–0.85), respectively. Patients in the intermediate (HR 0.51, P = 0.002) and high (HR 0.28, P < 0.001) pr-OS categories were at statistically significant lower risk of death compared with those in the low pr-OS category. Higher rate of Choi partial tumour responses were detected in intermediate pr-OS category. Tumour response according to Choi but not to RECIST criteria stratified patient survival of pr-OS categories, particularly for patients with intermediate to low pr-OS. Analyses conducted for 10-year inc-DM were consistent with results for pr-OS for prognostic value of Sarcuator predictions and Choi tumour response.

Interpretation: Sarcuator identifies variations in outcomes of high-risk STS treated with perioperative chemotherapy and improve prognostic classification, which is also associated with different patterns of tumour response, an outcome that further stratifies survival particularly for patients predicted at higher risk. Future trials investigating neoadjuvant chemotherapy should consider prognostic tool for selecting patients to be enrolled.

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1. Introduction

Soft tissue sarcoma (STS) of extremity and trunk wall are considered at high risk of disease progression when harbouring adverse prognostic features, such as large size and high malignancy grade [1]. Standard treatment includes combination of surgery and radiotherapy [2–5]. Anthracycline-based neoadjuvant and adjuvant systemic therapies have been tested to reduce risk of metastatic spread after these local treatments in several randomised controlled trials (RCT) [6,7]. These studies enrolled a mixed sarcoma patient population with variation in outcomes and showed a survival benefit ranging between 5 and 10%, which has been considered unsatisfactory particularly when balanced against meaningful high-grade toxicity [6]. Clinicians' opinions and clinical practice guidelines reflect this uncertainty suggesting that perioperative chemotherapy should be discussed with patients with high-risk tumours [4,5]. Recently, a RCT which enrolled a more homogeneous population and compared optimal neoadjuvant epirubicin and ifosfamide with several histology-based chemotherapy schedules dosages failed to demonstrate superiority of this latter approach [8]. Participants with high-risk STS of extremities and trunk wall treated with anthracycline-based chemotherapy had a 24%

improvement in disease-free survival and a 25% improvement in overall survival. These results, although needing further confirmation, underlined the importance of selecting a homogeneous sarcoma population when investigating perioperative treatment strategies.

Recent advances in patient staging further support efforts for improving selection of patients for perioperative treatments [9]. The 8th edition of the TMN staging system for sarcomas [10], which included prognostic nomograms [11], can improve patient risk stratification. In particular, prognostic tools potentially inform physician choice on treatment to be performed on a single patient [12]. Since Kattan *et al.* [13] tested the first nomogram for sarcoma, several other tools have been created and validated [11]. Among them, the Sarcuator includes a nomogram for extremity STS that predicts probability of overall survival and incidence of distant metastasis at 5 and 10 years after surgery based on patient age and tumour histology, size and grade [14].

In this study, we stratified prognostic risk of currently defined high-risk STS patients, who have large and high-grade tumours and are considered for perioperative chemotherapy, and also investigated chances of developing a tumour response. The prognostic nomogram Sarcuator [14] was used to predict overall survival (OS) probability and incidence of distant metastasis (DM) in

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