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Post-metastasis survival in extremity soft tissue sarcoma: A recursive partitioning analysis of prognostic factors

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Disease-free interval

Abstract ***Background:*** Recursive partitioning analysis (RPA) enables grouping of patients into homogeneous prognostic groups in a visually intuitive form and has the capacity to account for complex interactions among prognostic variables. In this study, we employed RPA to generate a prognostic model for extremity soft tissue sarcoma (STS) patients with metastatic disease.

Methods: A retrospective review was conducted on 135 patients with metastatic STS who had undergone surgical removal of their primary tumours. Patient and tumour variables along with the performance of metastasectomy were analysed for possible prognostic effect on post-metastatic survival. Significant prognostic factors on multivariate analysis were incorporated into RPA to build regression trees for the prediction of post-metastatic survival.

Results: RPA identified six terminal nodes based on histological grade, performance of metastasectomy and disease-free interval (DFI). Based on the median survival time of the terminal nodes, four prognostic groups with significantly different post-metastatic survival were generated: (1) group A: low grade/metastasectomy; (2) group B: low grade/no metastasectomy/DFI $\geqslant$ 12 months or high grade/metastasectomy; (3) group C: low grade/no metastasectomy/DFI $<$ 12 months or high grade/no metastasectomy/DFI $\geqslant$ 12 months; and (4) group D: high grade/no metastasectomy/DFI $<$ 12 months. The 3-year survival rates for each group were: group A, 76.1 $\pm$ 9.6%; group B, 42.3 $\pm$ 10.3%; group C, 18.8 $\pm$ 8.0%; and group D, 0.0 $\pm$ 0.0%.

Conclusion: Our prognostic model using RPA successfully divides STS patients with metastasis into groups that can be easily implemented using standard clinical parameters.

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1. Introduction

Soft tissue sarcoma (STS) represents a group of cancers that exhibit mesenchymal differentiation, accounting for approximately 1% of all adult malignancies [1–3]. STSs tend to metastasise in an early stage, mainly hematogenously with a predilection for the lungs and less frequently metastasise to liver and bone [2,4] Lymphogenic spread is relatively uncommon in STS [5], except for certain histological types such as the rhabdomyosarcomas, synovial sarcomas and epithelioid sarcomas [6,7]. About 10% of patients presents with metastatic disease [2,5,8], and almost one-quarter of patients with localised disease develop metastases in due course [2,9,10].

In general, prognoses of patients with metastatic STS remain poor, with the 3-year survival rate of 20–30% [11,12]. However, prolonged survival has been demonstrated in some patients, particularly in those with metastases amenable to resection. Although several clinicopathological parameters, such as histological grade, tumour size, disease-free interval and resectability have been suggested to be predictive of survival in metastatic STS, a better prognostication of metastatic STS is needed to guide decisions regarding adjuvant therapy and surveillance [13–16]. Estimating the aggregate risk based on the presence or absence of multiple factors is warranted, preferably using readily available clinicopathological parameters.

In this regard, we sought to generate a prognostic model for STS patients with metastatic disease using recursive partitioning analysis (RPA). RPA enables grouping of patients into homogeneous prognostic groups based on multiple variables and provides an easily interpretable method for classifying patients [17,18]. In this study, we employ RPA to divide STS patients with metastatic disease into clinically useful prognostic groups.

2. Patients and methods

2.1. Patients

From the prospectively collected database of our institute, 476 consecutive patients who had undergone surgical removal of extremity STS from February 1995 to May 2011 were reviewed. Among these 476 patients, we identified 153 (32.1%) patients with metastatic disease, who either presented with ($n = 55$) or developed ($n = 98$) metastases during follow-up. Of the 153 patients, patients with a follow-up duration shorter than 6 months ($n = 8$) and patients with isolated lymph node metastasis ($n = 10$) were excluded, which left 135 patients for analysis. In patients with systemic metastasis and lymph node metastasis, lymph node metastasis was regarded as locoregional disease, not as a metastasis [19,20]. The mean follow-up duration was 18.9 ± 18.9 months. The institutional review board of our institute approved this study.

2.2. Prognostic variables

Medical records were reviewed for the potential clinicopathological factors that might influence post-metastatic survival in STS: (1) patient demographics, (2) factors related to the primary tumour, (3) pattern of metastasis and (4) treatment of metastasis.

For demographic data, patients' gender, age and period of diagnosis were investigated. There were 85 males (63%) and 50 females (37%). The mean age at the time of metastasis was 49 years (range, 11–92 years). The patients' ages were dichotomised as <50 years and $\geqslant 50$ years for analysis. Forty-six patients (34%) presented after an unplanned removal of a STS before the correct histological diagnosis was made, without regard for the necessity to remove a margin of normal tissue surrounding the tumour.

For factors related to the primary tumour, anatomical site, histological diagnosis, histological grade, tumour size and tumour depth were investigated. Anatomical site of primary tumour was classified as upper extremity ($n = 37$, 27%) or lower extremity ($n = 98$, 73%), and as proximal extremity ($n = 93$, 69%) or distal extremity ($n = 42$, 31%). Most common histological diagnoses were undifferentiated pleomorphic sarcoma (UPS, $n = 34$), synovial sarcoma ($n = 23$), liposarcoma ($n = 15$) and leiomyosarcoma ($n = 12$). As for histological grading of the primary tumour, there were four grade 1 (3%), 56 grade 2 (42%) and 70 grade 3 (52%) tumours according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) classification system [21,22]. Size of the primary tumour, defined as the largest diameter on the pathological examination report or preoperative magnetic resonance imaging (MRI), was 9.8 cm (range, 1.1–35.0 cm). For the purpose of analysis, tumour size was dichotomised by a cut-off value of 5 cm. Tumours located exclusively above the superficial fascia were defined as superficial. Tumour depth could be determined in 128 patients (95%) with nine superficial and 119 deep tumours. All primary tumours were resected and pathologically negative surgical margins were achieved in 112 patients (83%). Postoperative radiation therapy was administered in 79 patients (59%), all of whom received external beam radiation with the median dose of 60 Gy (range, 50–65 Gy). Postoperative chemotherapy was administered in 21 patients (23%). For surveillance for distant metastasis, chest imaging and bone scans were performed every 3–4 months for 2 years, then every 6 months for the next 3 years, and then annually. Imaging of the primary site was done with MRI or ultrasound based on the risk of local recurrence.