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Identification of low-risk tumours in histological high-grade soft tissue sarcomas

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ABSTRACT

In more than one-third of patients with a histological high-grade malignant soft tissue sarcoma metastasis develops despite local control of the primary tumour. Hence, adjuvant chemotherapy is increasingly used for these relatively chemoresistant tumours which requires improved prognostication to exclude low-risk patients from overtreatment. We assessed the value of stepwise prognostication in a series of 434 histological high-grade STS of the extremity and trunk wall. Vascular invasion was used as the first discriminator whereafter the risk factors tumour necrosis, size (>8 cm) and infiltrating growth pattern were used to discriminate high- and low-risk tumours. We identified a high-risk group with a cumulative incidence of metastasis >0.4 at 5 years, and a low-risk group, comprising half of the tumours, with a cumulative incidence of metastasis <0.15. The model was validated in an independent material of 175 patients. This model improved prognostication in STS and is of value for identifying patients who probably should not receive adjuvant chemotherapy.

1. Introduction

One-third of adult patients with soft tissue sarcomas (STS) of the extremity and trunk wall without detectable metastases at the time of diagnosis will die of metastatic disease despite local control of the primary tumour.[1,2] Therefore, adjuvant chemotherapy is increasingly used in patients considered having highly malignant tumours. However, there is no consensus on how to best identify high-risk tumours; several systems have been suggested, but few have been validated. The two most commonly used, and also validated, systems are the French FNCLCC system and the American AJCC/UICC system.[3–5] Patients with localised tumours at diagnosis but with the highest risk for metastasis (Stage III) in the AJCC/UICC system comprise half of the STS population with about 50% metastatic risk,[4] the corresponding figure in the FNCLCC (Grade 3) is about half the sarcoma population with almost a 60% risk of metastatic disease.[3] These patients are often considered for chemotherapy. In both systems almost half of the tumours are classified as Stage II/Grade 2 with a 30%

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risk for metastasis; whether these patients should be candidates for adjuvant systemic treatment is unclear.

We constructed a prognostic system based on a stepwise use of risk factors; first vascular invasion and thereafter a combination of the risk factors tumour size, necrosis and growth pattern was applied in the remaining tumours without demonstrated vascular invasion. This system was established in a series of 434 histological high-grade STS of the extremities and trunk wall and was then validated in an independent material of 175 tumours. Our aim was to improve the identification of patients who manage well without chemotherapy despite having histological high-grade soft tissue sarcomas.

2. Patients and methods

2.1. Patients

Common for all patients in all series was >15 years of age, primary, pathology peer-reviewed histological high-grade soft tissue sarcoma of the extremity or trunk wall, no metastases, treatment at a sarcoma centre, no chemotherapy and complete follow-up (Table 1).

2.1.1. Test series

This series included 434 patients treated between 1986 and 2004 at tumour centres in Sweden and Norway.[6] The surgical resection margin was wide or marginal in 398 (92%), and intralesional in 36 (8%) tumours. Radiotherapy was administered to 119 (27%) patients. Metastases developed in 135 (31%) patients and a local recurrence occurred in 87 (20%) patients. The median follow-up time for survivors without metastasis was 10 years.

2.1.2. Validation series

The prognostic system suggested from the test series was validated in an independent series of 175 tumours: 122 patients treated at the Lund University hospital, Sweden, 1988–2001 and 53 patients treated at the The Norwegian Radium Hospital 1998–2001 (series A and B, Table1). The Swedish series has previously been published as part of 140 STS comprising of 18 histologically low-grade malignant tumours and the 122 high-grade malignant tumours.[7]

The surgical resection margin was wide or marginal in 168 tumours and intralesional in 7 tumours. Radiotherapy was administered to 70 (40%) patients. Metastasis developed in 64 (37%) patients and 28 (16%) had a local recurrence. The median follow-up for survivors without metastasis was 5 years.

The present study was approved by the Lund University Ethics Committee.

2.2. Pathology review

The peer review in the test series of 434 tumours focused principally on subtyping the sarcoma and on attributing a histological malignancy grade and was based on small tumour sections (7–10 slides per tumour). Appropriate immunohistochemical panels were used for establishment of cell lineage and also cytogenetic techniques, and sometimes electron microscopy.[8–10] Malignancy grading used a IV-tiered grading system based on cellularity, pleomorphism, nuclear atypia, tumour necrosis and mitotic activity. In this system, Grades III–IV corresponds roughly to Stages II–III in the AJCC/UICC system and to Grade 3 in the FNCLCC system.[3,11,12] Necrosis was determined as present or not, the amount of necrosis was not quantified and thus we could not grade our tumours according to the FNCLCC system.

The 53 tumours in the Norwegian part of the validation series were reviewed by two of the authors (B.B. and P.R.) and necrosis, vascular invasion and growth pattern were determined on multiple tumour sections (10–15 slides per tumour).

The 122 tumours in the Swedish part of the validation series had been histologically evaluated using 7–10 small sections for immunohistochemical staining and whole-tumour sections, i.e. entire tumour planes had been thoroughly assessed for vascular invasion and presence of necrosis.[7] This means that the most intense search for necrosis and vascular invasion using most tumour material (whole tumour sections) was performed in this series.

2.3. Definition of prognostic factors

Tumour size was measured as the maximum diameter (cm) on the fresh surgical specimen in the test series and in series C, but in series B on a formalin fixed surgical specimen.

Tumour necrosis was defined as the presence of amorphous cellular debris, usually associated with a neutrophil polymorphonuclear cell response, or clustering of dead cells and apoptotic bodies or cell ghosts. We employed no lower limit of a necrotic area, but areas of hyalinosis or oedema, fibrin exudates lacking tumour cells or acellular areas of fibrosis were not defined as necrosis.

Vascular invasion of tumour cells was defined as the presence of tumour cells within any space having an obvious endothelial lining, whether within the tumour or in the tumour rim. The tumour cells had to be adherent to the vessel wall, or associated with adherent fibrin, red blood cells, or leucocytes. Bulging of tumour into a vessel with intact endothelial lining was not accepted as intravascular tumour growth.

Peripheral tumour growth pattern was microscopically assessed in the tumour periphery on an entire tumour plane if a whole-tumour section had been performed (validation series A), and from serial small sections from the tumour in the test series and validation series B. The growth pattern was classified as pushing if no sign of infiltrative growth could be seen, and as infiltrating if the tumour rim was seen infiltrating into the surrounding tissues.

2.4. Modelling the prognostic system

The purpose of our study was to find a prognostic system that separates patients with histological high-grade STS but with a low risk for metastasis without chemotherapy from high-risk patients. The patients age at diagnosis was high and thus death due to any cause was considered a competing event to the end-point metastasis.[13] Very few metastases occurred after 5 years, and hence the cumulative incidence of metastases at 5 years was chosen as the end-point.[13] Hazard ratios for