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Improved prognostication in soft tissue sarcoma: independent information from vascular invasion, necrosis, growth pattern, and immunostaining using whole-tumor sections and tissue microarrays☆

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Summary In 140 mixed primary soft tissue sarcomas with a median follow-up of 6 years, the prognostic importance of tumor size, tumor depth, grade, necrosis, vascular invasion, and peripheral growth pattern (pushing versus infiltrating) was evaluated on whole-tumor sections. Immunohistochemical expression of Ki-67, p53, cyclin A, bcl-2, β-catenin, CD44, and P-glycoprotein was determined using tissue microarray from the peripheral growth zone. Local recurrences developed in 17% of the patients and correlated with necrosis, vascular invasion, and cyclin A expression. No local recurrence developed in tumors with a pushing growth pattern, regardless of tumor grade and depth. Metastasis developed in 39% of the patients. Vascular invasion was identified in 36% of the tumors and was the strongest prognostic factor for metastasis with a hazard ratio of 3.5. Growth pattern and tumor necrosis were also strong prognostic factors for metastasis, whereas malignancy grade, tumor size, and tumor depth did not have any independent prognostic value. Immunostaining showed independent prognostic information for Ki-67, β-catenin, CD44, and P-glycoprotein. The results indicate that whole-tumor sections could facilitate identification of vascular invasion, necrosis, and peripheral growth pattern and that immunohistochemical profiling from the growth zone also provides independent prognostic information for metastasis in soft tissue sarcoma.

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1. Introduction

Adult soft tissue sarcomas (STSs) of the extremities and trunk wall comprise less than 1% of all malignant tumors and consist of more than 50 histopathologic subtypes [1,2]. Surgery, often combined with radiotherapy (RT), is the primary treatment, whereas the role of chemotherapy is unclear except for the rare rhabdomyosarcoma and Ewing sarcoma/primitive neuroectodermal tumor of soft tissue [3-6]. Local recurrences (LRs) are seldom lethal in STS of the extremities or trunk wall, but often cause considerable morbidity and occur in up to 20% of the patients with long-term follow-up [5-8]. Strong prognostic factors for LR are high histological malignancy grade and marginal resection without adjuvant RT [8]. Highly malignant STSs are generally thought to infiltrate surrounding tissues, which explain their propensity for LR [4]. However, there is a lack of systematic studies of the peripheral growth patterns in STS.

Despite local control, disseminated disease, most commonly as lung metastasis, develops in about one third of the patients [7]. A multitude of prognostic factors for metastasis in STS have been proposed, and the most consistent strong factors are tumor size, tumor depth, histological malignancy grade, presence of vascular invasion, and tumor necrosis [9-11]. Most prognostic systems are based on combinations of tumor size, tumor depth, and malignancy grade [12]. Tumor size and tumor depth are usually easily determined, whereas histological malignancy grade, despite being a strong prognostic factor, is not uniformly interpreted, and there is no consensus as to whether a 2-, 3-, or 4-tiered scale should be used [13,14]. Furthermore, the rates of vascular invasion and necrosis in STS vary considerably between different studies [7,9,11].

We have investigated the value of using whole-tumor sections for assessment of tumor-related prognostic factors in 140 STS and also correlated the peripheral tumor growth pattern to LR and metastasis. We used the tissue microarray (TMA) technique to study the prognostic value of the immunohistochemical (IHC) expression of Ki-67, p53, cyclin A, bcl-2, β-catenin, CD44, and P-glycoprotein (Pgp) in the tumor peripheral growth zone.

2. Materials and methods

2.1. Patients

From 1988 through 2000, 298 adult patients with primary, unoperated, nonmetastatic STS located in the extremities or the trunk wall were referred to the Musculoskeletal Tumor Centre at the Lund University Hospital. Of these, 262 patients were surgically treated without preoperative RT or chemotherapy, and whole-tumor paraffin blocks were established from 140 (54%). Histopathologic diagnosis was made by experienced sarcoma pathologists (members of the Scandinavian Sarcoma Group peer review group) based on the current reference works [1,2,15]. Appropriate IHC panels were used for establishment of cell lineage and also cytogenetic techniques. In difficult cases, international second opinion was sought. There were no differences regarding clinicopathologic factors (age, tumor size, tumor depth, histotype) in patients from whom whole-tumor sections had been made or not. There were 12 different histotypes in the series, with leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma (MFH), and myxofibrosarcoma representing the majority (Table 1). Malignancy grading was based on a 4-tiered grading system that included cellularity, pleomorphism, nuclear atypia, tumor

Table 1 Clinical-pathological data in 140 STS

Sex, n (%)	
Male	79 (56)
Female	61 (44)
Median (range) age (y)	69 (16-94)
Site, n (%)	
Trunk wall	10 (7)
Upper extremity	28 (20)
Lower extremity	102 (73)
Median (range) size (cm)	8 (2-28)
Depth, n (%)	
Superficial	47 (34)
Deep-seated	91 (66)
Histopathologic diagnosis	
Leiomyosarcoma	46 (33)
Liposarcoma	19 (14)
MFH	18 (13)
Myxofibrosarcoma	18 (13)
STS NOS	12 (9)
MPNST	10 (7)
Synovial sarcoma	8 (6)
Extraskeletal myxoid chondrosarcoma	3 (2)
Myofibroblastic sarcoma	2 (1)
Angiosarcoma	2 (1)
Fibromyxoid sarcoma	(0.5)
Malignant mesenchymoma	1 (0.5)
Histological malignancy grade, n (%)	
1	5 (4)
2	13 (9)
3	24 (17)
4	98 (70)
Tumor necrosis, n (%)	83 (59)
Vascular invasion, n (%)	50 (36)
Infiltrating peripheral growth pattern, n (%)	100 (71)
Quality of local treatment, n (%)	
Adequate	124 (89)
Inadequate	16 (11)
Adjuvant chemotherapy	8 (6)
LR	24 (17)
Metastasis	54 (39)

NOTE. Sixteen patients developed both LR and metastasis. Abbreviations. NOS, not otherwise specified; MPNST, malignant peripheral nerve sheath tumor.