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Synovial sarcoma in children and adolescents: A critical reappraisal of staging investigations in relation to the rate of metastatic involvement at diagnosis

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Abstract *Background:* European protocols for paediatric synovial sarcoma (SS) require that all children routinely undergo chest computed tomography (CT) scanning and bone scanning as initial staging procedures. This study aims to determine the rate of initial metastases in paediatric SS based on specific clinical characteristics, thereby investigating whether these diagnostic procedures are really necessary in all patients.
Methods: Data on 258 previously-untreated SS patients <21 years old were pooled from the databases of different European paediatric groups (study period 1988–2005) for this analysis, and the associations between patients' characteristics and any presence of metastasis were estimated.
Results: Fifteen cases (5.8%) had distant metastases at diagnosis (86% pulmonary). The presence of metastases was unassociated with patients' gender or age, tumour grade or site, but it

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was influenced by T-status, and especially primary tumour size: the risk of metastases was 32 times higher in cases of tumour >5 cm than for tumours ⩽5 cm.
Conclusions: Our findings suggest that tumour diameter can be used as a variable for identifying patients at greater risk of metastases and warranting more accurate radiological investigations. Chest CT scanning may improve the accuracy of pulmonary staging over X-ray, but requires different ionising radiation exposures that might have carcinogenic potential: it can be omitted for patients with tumours ⩽5 cm. Given the very low risk of bone metastases, bone scans may be recommended only in cases with evidence of lung metastases.

1. Introduction

Synovial sarcoma (SS) is a typical sarcoma subtype crossing between the paediatric and adult age groups, and it represents the most common non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in childhood.[1] Historically, relatively high rates of response to chemotherapy were recorded in paediatric series (i.e. approximately 60%), so SS was traditionally considered a 'rhabdomyosarcoma (RMS)-like' tumour by paediatric oncologists, particularly in Europe. Children were thus enrolled in RMS protocols and treated with the same diagnostic and therapeutic approach as for RMS patients. SS is biologically and clinically different from RMS, however.[1–6] RMS in fact is a highly aggressive tumour that tends to disseminate along haematogenous routes, and it should practically be assumed that all cases will present with micrometastatic disease at diagnosis. Staging investigations can identify distant metastases in about 20% of RMS cases, the lung being the most common site involved.[7,8] Given its definition as an 'RMS-like' tumour, SS patients enrolled in European paediatric RMS protocols routinely underwent assessment for distant metastases, which implied chest computed tomography (CT) scanning, technetium bone scanning, abdominal ultrasound (or CT), and bone marrow aspiration plus trephine biopsy, to identify lung, bone, abdominal and bone marrow dissemination, respectively. In the current European paediatric Soft tissue sarcoma Study Group (EpSSG) trial dedicated to SS (the NRSTS 2005 protocol), chest CT and bone scans are still considered mandatory for all SS patients.[9]

Published paediatric SS series indicate a risk of metastatic involvement at diagnosis of around 5–7%, however,[2–4] while the Surveillance, Epidemiology, and End Results (SEER) database (1983–2005) identified 11% of the registered children/adolescents as having metastatic disease[1] – a rate that is definitely lower than the one reported for RMS. Hence our decision to pool the data in the databases of the European paediatric groups currently involved in the EpSSG study, with a view to ascertaining the rate of initial metastases in cases of SS based on specific clinical characteristics, and thereby to investigating whether all the currently-used diagnostic procedures are really necessary in all patients.

2. Material and methods

The study concerned a series of 258 previously-untreated patients with a diagnosis of SS, prospectively registered in the databases of the Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee (AIEOP-STSC)[4] (63 patients, 16 registered in the RMS'88, 44 in the RMS'96 and 3 in the RMS4'99 protocols), the Istituto Nazionale Tumori (INT) of Milan, Italy,[3] before 1996 (in 1996 the INT joined the national protocols) (31 patients), the United Kingdom Children's Cancer and Leukaemia Group (UKCCLG) (60 cases),[5] and the International Society of Pediatric Oncology (SIOP) Malignant Mesenchymal Tumor (MMT) group (104 cases, 32 from the MMT89, 70 from the MMT95 and 2 from the MMT98 trials).[6]

The inclusion criteria for the study were: (1) study period: 1988–2005; (2) patient's age 0–21 years; (3) histological diagnosis of SS; (4) all tumour sites; (5) no pre-treatment (apart from initial resection).

The pre-treatment clinical findings considered were: gender; age; tumour site, defined as extremities (including the limb girdles, i.e. the inguinal region, hip, buttock, shoulder, and axillary region) or axial sites, i.e. head and neck, lung and pleura, retroperitoneum, trunk (thoracic and abdominal wall); tumour size (less or more than 5 cm); histological subtype and grade; T (T1 or T2 in relation to local invasiveness, TA or TB according to tumour diameter ⩽ or >5 cm), N and M status, according to the clinical TNM system[10]; site of metastases. Since arrangements for a central pathology review were already in place within each collaborative group, the histological diagnoses were not re-reviewed specifically for this analysis. Grading was not available for the majority of cases because in the past it was not assessed routinely in SS, and because histological diagnoses were obtained in most cases on biopsy specimens, which were not suitable for any definition of tumour grade in many cases (while the specimens from delayed surgery were inappropriate for grading due to prior chemotherapy). When available, grades were assigned according to the French Federation of Cancer Centers Sarcoma Group's (FNCLCC) system.[11,12] The $t(x;18)$ and SYT-SSX transcript analyses were available for a minority of cases.