Diagnosis, treatment and prognosis of patients with synovial sarcoma

The Scandinavian Sarcoma Group experience

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Soft tissue sarcoma accounts for approximately 1% of all malignant tumors and synovial sarcoma less than 10% of these (Cadman et al. 1965). In contrast to other soft tissue sarcomas, synovial sarcoma is commoner among younger persons. The treatment has been surgical, sometimes with postoperative adjuvant radiotherapy to improve local control. Adjuvant chemotherapy is often given to children, but its value is unknown.

The clinical course after surgical treatment varies from immediate cure to development of early metastases, most often located in the lungs. The reported 5–year overall survival rates range from 40% to 70% (Cadman et al. 1965, Choong et al. 1995). Whereas metastases after 5 years are very uncommon among most soft tissue sarcomas, such late recurrences are well known features of synovial sarcoma. Hence, the reported survival rates of these patient have dropped to 30–50% at 10 years (Wright et al. 1982, Choong et al. 1995). Although they continue to improve it remains unclear whether this is due to a change in the selection of patients or changes in treatment.

Our study was based on patients in the SSG Central Register and the Swedish National Cancer Register with primary synovial sarcoma in the extremities or trunk wall, diagnosed between 1986 and 1994. Hence, the Swedish patients may be regarded as a population–based cohort. They all underwent surgery for the primary tumor. Patients with metastases at diagnosis were excluded, leaving 104 patients for study. Clinical data were reexamined and brought up to date by study of medical charts and visits to the various centers. We present preliminary data about the clinical course and immunohistochemical analyses the background to studies regarding histopathology, Comparative Genomic Hybridization and RT–PCR of synovial sarcoma.

Clinical study

We evaluated the findings in 104 surgically treated patients with synovial sarcoma treated 1986–94. The median follow–up of survivors was 6 (2–11) years. 34 patients developed metastases. The overall 5– and 7–year survival rates were 0.76 and 0.69, respectively.

Tumor size is a well recognized prognostic marker of synovial sarcoma (Wright et al. 1982, Choong et al. 1995), age (Wright et al 1982), gender (Moberg et al. 1968) and site (Hajdu et al. 1977) have also thought to be of prognostic importance. In our study, large tumor size and amputation were associated with impaired metastasis–free survival. In addition, patients with a local recurrence and a higher risk of metastases after the local event. Local excision with inadequate margin was associated with a higher risk of local recurrence.

Histopathological analysis

The prognosis of synovial sarcoma has been associated with histopathologic factors, such as subtype (Hajdu et al. 1977), mitotic rate (Singer et al. 1996), percent glandularity (Cagle et al. 1987) and tumor necrosis (Oda et al. 1993). The *biphasic* subtype is thought by some to have a better prognosis than the *monophasic* type. However, there is no consensus about what is a true monophasic and biphasic synovial sarcoma. Recently, another classification has been introduced, *poorly versus non–poorly differentiated* synovial sarcoma. Poorly differentiated synovial sarcomas are associated with a very poor prognosis (Enzinger and Weiss, 1995). Most poorly differentiated tumors fall into the monophasic category and this may explain why earlier investigations have revealed a worse prognosis for the monophasic subtype.

The SSG Pathology Board consists of a selected group of pathologists from the participating centers. The reexamined all available original slides from the primary tumors, without knowledge of the clinical course. The histopathological criteria for synovial sarcoma were those of Enzinger and Weiss (1995).

Comparative genomic hybridization (CGH)

80 tumors were with CGH in Helsinki at the Department of Medical Genetics, Haartman Institute, regarding the prognostic importance of secondary genetic changes besides translocation t(X;18) (p11.2; q11.2) (Turc–Carel et al. 1987). Hitherto, the significance of secondary genomic changes has not been reported in a large number of synovial sarcoma patients.

Immunohistochemical markers

The p53 gene, a tumor suppressor gene, is believed to play an active role in cell growth control (Raycroft et al, 1990) by acting as a regulatory checkpoint in the cell cycle, arresting the cells in G_1 phase if DNA damage has occurred (Yin et al, 1992). In contrast, mutated p53 fails to block cell cycle progression (Nigro et al, 1989). Therefore, p53 mutations may contribute to uncontrolled cell growth. Since the mutated product has a considerably longer half–life than germ line p53, leading to accumulation of the suppressor oncogene product, p53 mutations can be assayed with immunohistochemistry (Finlay et al, 1988). Ki–67 is an antigen exclusively expressed during the proliferating phase of the cell cycle (Gerdes et al, 1984). The function of Ki–67 is still unknown, but it is a well established marker of proliferation. Since MIB–1 index, a true Ki–67 equivalent, recognizes all phases of the cell cycle (not in G_0), it is a much more sensitive proliferation marker than the mitotic index.

The prognostic significance of both these markers in soft tissue sarcomas remains unclear, mainly because of the small amount or heterogeneous material. The purpose of this study is to analyze the prognostic importance of the proliferation index, measured with the MIB–1 monoclonal antibody, and the expression of p53 in a large number of clinically and histopathologically well–characterized synovial sarcoma patients. The data are based on formalin–fixed paraffin–embedded material from 86 patients with primary synovial sarcoma. Two risk factors for metastases have been identified: increasing tumor size and MIB–1 $\geq$10%, whereas p53–expression is not a risk factor. The discrimination between patients with a good or a poor prognosis is feasible, based on tumor size and MIB–1 index alone.

RT–PCR

Cytogenetic studies of synovial sarcoma have revealed a characteristic translocation, t(X;18)(p11.2)(q11.2) (Turc–Carel et al. 1987), in more than 90 % of all tumors. In some tumors, this is the sole detectable cytogenetic abnormality. Two chimeric proteins have been identified, from the fusion of the *SYT* gene on chromosome 18 to either the *SSX1* gene or the *SSX2* gene located on the X chromosome (Clark et al. 1994; Leeuw et al. 1994). Hitherto, only one study has attempted to determine the influence of the two alternative forms of the *SYT–SSX* fusion gene on clinical outcome Kawai et al. (1998) found that tumors with *SYT–SSX2* fusion transcript than *SYT–SSX1* were associated with a higher metastasis–free survival rate. This is surprising because *SYT–SSX* is mainly found in monophasic tumors, which were previously regarded as having a worse prognosis than biphasic tumors. In our study, we shall address the same issue but also look for and characterize possible new breakpoint areas.

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