# Synovial sarcoma

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**Abstract**
*Synovial sarcoma (SS) is a rare and aggressive soft tissue tumor, which accounts for 7-8 % of all human malignant sarcomas. Although this tumor generally affects adults, about 30% of reported cases occur in children and adolescents. Despite its name, SS does not appear to be of synovial origin, but rather from multipotent stem cells that differentiate into mesenchymal and/or epithelial structures. Clinically, SS appear as deep-seated, painless, slowly growing masses. Most frequently the tumor affects lower and upper extremities, especially in periarticular regions of large joints. The etiology of the disease remains unknown. Almost all SS cells are characterized by the presence of a translocation involving chromosomes X and 18 [t(X;18)(p11.2;q11.2)]. This translocation is specific to SS and constitutes an excellent tool to diagnose this malignancy. The optimal approach to treatment of SS remains undefined. Complete surgical removal of the primary tumor is the mainstay of treatment. Adjuvant radiotherapy appears to be beneficial in the treatment of microscopic residual disease after surgery. The role of chemotherapy needs to be clarified.*

**Key-words**
Synovial sarcoma, soft tissue tumor, periarticular regions, SYT-SSX fusion proteins.

## Disease name

The term synovial sarcoma (SS) was coined to denominate tumors arising near tendon sheats and joint capsules. Despite its name, SS does not appear to arise from the synovial membrane, but rather from as yet unknown multipotent stem cells that are capable of differentiating into mesenchymal and/or epithelial structures (Fisher, 1994; Smith *et al.*, 1987) and lack synovial differentiation (Sandberg *et al.*, 2002).

## Definition/Diagnostic criteria

SS is a soft tissue sarcoma usually divided into three subtypes: biphasic, monophasic and, as recently described, poorly differentiated SS (Enzinger *et al.*, 1995).

The biphasic type contains epithelial and spindle cell elements, which occur in varying proportions.

In contrast to biphasic type, monophasic SS contains only spindle cells (Coffin, 1997).

Poorly differentiated SS share some typical morphologic features of monophasic or biphasic

SS, but has also a variable proportion of poorly differentiated areas characterized by high cellularity, pleomorphism and polygonal or small round-cell morphology, numerous mitoses, and often necrosis.
All morphological subtypes are characterized by a specific t(X;18)(p11.2; q11.2) chromosomal translocation.

**Differential diagnosis**
Like other soft tissue sarcomas, SS is difficult to recognise purely on the basis of histological appearance. In most cases, these tumours can be unambiguously identified only by immunohistochemical analysis, ultrastructural findings and demonstration of the specific chromosomal translocation.
Biphasic SS may be difficult to distinguish, especially when the tumor arises in an unusual location or when the epithelial component is absent. Immunohistochemical staining of keratins and/or the Ber-Ep4 epithelial antigen (Latza *et al.*, 1990) may be used to distinguish SS from, for example, fibrosarcoma (Krall *et al.*, 1981), or malignant mesothelioma (Helliwell *et al.*, 1995; Nicholson *et al.*, 1998).
Monophasic SS may be misdiagnosed as a fibrosarcoma, leiomyosarcoma, hemangiopericytoma or malignant peripheral nerve sheat tumor. In monophasic SS, immunohistochemistry generally demonstrates epithelial markers positivity (*e.g.* keratins and EMA), not seen in fibrosarcoma (Miettinen, 1991), muscle-associated markers (*e.g.* desmin and smooth-muscle actin) and S-100 protein negativity, allowing a differential diagnosis from leiomyosarcoma and malignant peripheral nerve sheat tumors, respectively (Lopes *et al.*, 1994). Poorly differentiated SS may be distinguished by the expression of CD56, CD99 and high-molecular-weight cytokeratins (Folpe *et al.*, 1998).
Also, the BCL-2 protein has been suggested to be helpful in the differential diagnosis of SS, but further studies are necessary to confirm its potential diagnostic role (Miettinen *et al.*, 1998). However, the characteristic t(X;18)(p11.2;q11.2) chromosomal translocation represents a specific and a strong indicator for the diagnosis of SS, regardless of the histological subtypes.

**Etiology**
The etiology is unknown. Almost all SS cells are characterized by a translocation fusing two genes, *SYT*, located to chromosome 18q11 and *SSX1*, *SSX2* or *SSX4* located to the Xp11 breakpoint (de Leeuw *et al.*, 1994; Clark *et al.*, 1994; Crew *et al.*, 1995). The mechanism by which the SYT-SSX fusion protein provide malignant potential to the cells remains unsettled. Tumors expressing the SYT-SSX1 fusion protein more often exhibit a biphasic histology, a higher proliferation rate and are associated with a poorer outcome. Recently, SYT and SSX proteins were found to be localized in the nucleus. They have been shown to be involved in protein-protein interactions that occur in signal transduction pathways, SYT as an activator of transcription and SSX proteins as transcriptional repressors (dos Santos *et al.*, 2001).

**Clinical description**
A painless mass is the most common mode of presentation. The mass is present for several weeks with painless growing. The patient usually presents with a palpable and increasing mass but quite variable in size. Other modalities of presentation may occur: a pretumor phase of pain and tenderness without evidence of a mass; an involvement of an articular region with acute arthritis or bursitis; a contracture with chronic features; a mass noted after an episode of trauma (Coffin, 1997). The most common sites of disease are the extremities. The lower extremities appear more frequently affected than the upper extremities, often in the region of the thigh and knee. The periarticular regions are especially affected, usually in close association with tendon sheats, bursae and joint capsules but they rarely involve the articular surface (Coffin, 1997). However, there is a broad spectrum of locations including head, neck, trunk, lung, esophagus, intestine, mediastinum and retroperitoneum.
The major sites of metastatic spread are the lungs and, less often, regional lymph nodes, bone and bone marrow (Enzinger *et al.*, 1995). In children, lymph node involvement is more rarely seen.

**Diagnostic methods**
A definitive diagnosis can only be established by an adequate tissue biopsy, but radiological investigations may be useful to characterise this tumor. As described above, the characteristic cytogenetic translocation t(X;18)(p11.2;q11.2) is present in nearly all synovial sarcomas, providing strong evidence for the diagnosis of this tumor.

***Radiology***
About one third of SSs reveal calcifications that may be evident on radiographs or computed tomography (CT) scans. The tumor usually shows heterogeneous septate mass. Mixed cystic and solid appearance is common and may be due to the presence of haemorrhage and/or necrosis.

Magnetic resonance imaging (MRI) may be a more valuable examination because it provides greater contrast between tumor and normal tissue and can show neurovascular or regional lymphatic involvement. On MRI, the tumor appears sharply marginated and largely cystic or multilocated with various degrees of internal septations (McCarville *et al.*, 2002; Morton *et al.*, 1991). Because the tumor is often well defined and discloses a cystic appearance, SS is commonly misdiagnosed as benign on MRI.
Moreover, radiological investigations are important in the detection of metastatic disease. The presence of secondary spread influences both the prognosis and the management. A chest CT scan is used to detect pulmonary metastases. Metastatic disease to bone may also occur and these lesions can be demonstrated by isotope scintigraphy using bone-seeking isotope 99Tc.

***Histological examination***
The use of ultrastructural, immunohistochemical and cytogenetic studies enables a better characterisation of the biphasic, monophasic and poorly differentiated SS subtypes.

**Prognostic factors**
SS has traditionally been considered to be associated with a poor outcome. However, it has recently emerged that not all SSs present the same severe outcome. Various factors are reported to have an adverse prognostic significance, such as the presence of metastases, as well as the tumor's size (diameter greater than 5 cm.), invasiveness, high histological grade (based on the mitotic and tumor necrosis), positive surgical margins, and poor histological differentiation (Okcu *et al.*, 2003; Trassard *et al.*, 2001; Spillane *et al.*, 2000; McCarville *et al.*, 2002). Conflicting data have been reported on the prognostic value of sex, age at diagnosis, tumor location, and biphasic versus monophasic SS. Recently, some molecular genetic features such as the SYT-SSX fusion type or the presence of an increased levels of HER2/neu appear to influence positively the outcome of patients with SS (Nuciforo *et al.*, 2003; Sandberg *et al.*, 2002; Nilsson *et al.*, 1999; Kawai *et al.*, 1998). However, further studies are needed to better characterise the prognostic role of these molecular features.

**Epidemiology**
SSs are relatively rare tumors. This type of tumor accounts for 7% to 8% of all malignant soft tissue sarcomas and is the most common non-rhabdomyosarcoma soft tissue sarcoma in pediatric population (Enzinger *et al.*, 1995). SS most frequently occurs in young adults. Approximately 30% of SS are manifested during the first two decades of life with a median age of 13 years (Okcu *et al.*, 2003; Schmidt *et al.*, 1991). The male to female ratio usually shows a slight male predominance.
The annual incidence rate in the USA is 0.7 per million in children and adolescents younger than 20 years of age (Ries *et al.*, 1999). Because SS in children is rare, single institution or co-operative series such as SIOP, St Jude Hospital or German CWS, consisted of a small number of patients (Stevens *et al.*, 2001; Pappo *et al.*, 1994; Ladenstein *et al.*, 1993). Recently, a multicenter retrospective analysis based on 219 pediatric patients has collected data from four research groups (Okcu *et al.*, 2003).

**Management**
The optimal treatment of SS in children remains undefined.
*Complete surgical excision* is the treatment of choice. However, SS often has a pseudocapsule that allows the tumor to shell out fairly easily, giving the false security of a total removal (Andrassy *et al.*, 2001). The difference between complete local resection and wide tumor resection appears to influence significantly the outcome (Lewis *et al.*, 2000; Brennan, 1997; Oda *et al.*, 1993; Blakely *et al.*, 1999). Positive microscopic margins have a greater likelihood of local recurrence associated with an increased risk of metastatic spread and decreased disease free-survival. Therefore, the operating surgeon should aim at negative surgical margins, although there is no clear evidence on the extent of the negative margins (Blakely *et al.*, 1999; Mullen *et al.*, 1994; Sadoski *et al.*, 1993). Primary re-excision of the tumor should be carefully considered in all patients with gross or residual tumor since the re-excision seems to decrease the risk of local recurrence (Andrassy *et al.*, 2001).
*Local radiotherapy* is often required to obtain a local control of the disease. Based on the results of limited series, radiotherapy appears to have a role in the treatment of patients with newly diagnosed SS, especially for children with minimal primary tumor following surgery (Carson *et al.*, 1981; Fontanesi *et al.*, 1996). However, there is no clear evidence that local irradiation is associated with better local control of the disease in patients with localised completely resected tumor and negative surgical margins. On the contrary, in patients with gross residual tumor after surgery, radiotherapy appears to significantly reduce local recurrence rates (Okcu *et al.*, 2003; Fontanesi *et al.*, 1996).
Although SS is a chemosensitive tumor, the role of *adjuvant chemotherapy* remains controversial.

Most regimens with combination of alkylating agents (cyclo- or iphosphamide) and anthracycline, have shown activity in patients with measurable disease but their real influence on survival remains debatable (Kampe *et al.*, 1993; Rosen *et al.*, 1994; Lewis *et al.*, 2000; Okcu *et al.*, 2003). The only prospective pediatric trial addressing the role of chemotherapy (vincristine-actinomycinD-cyclophosphamide versus observation) in non-rhabdomyosarcoma soft tissue tumors performed by Pediatric Oncology Group (POG), showed no substantial benefit on survival (Pappo *et al.*, 1999). A potential advantage is that chemotheraphy facilitates the implementation of secondary surgery with adjuvant radiotherapy in patients with gross residual tumor after surgery t (Okcu *et al.*, 2003). However, objective responses with high dose iphosphamide (14 to 18 g/m2) were reported by Rosen *et al.*, 1994. But these results were not confirmed by the meta-analysis on 2185 sarcoma patients performed by the European Organisation for Research and Treatment of Cancer (EORTC), although a lower dose of iphosphamide was administered (Van Glabbeke *et al.*, 1999).

The outcome for children with metastatic disease remains poor despite multiple chemotherapy regimens. The estimated 5-years survival rate for patients with localized completely resected or with microscopic residual disease is about 80 ± 9% compared with 17 ± 15% of children with gross residual tumor after surgery or distant metastases at the time of diagnosis (Pappo *et al.*, 1994).

Prospective randomised clinical trials with more effective agents are necessary to evaluate the benefit of adjuvant chemotherapy in the treatment of SS.

## Unresolved questions

Further studies are required to assess the role of molecular genetics of SS and to evaluate the possibility for targeted therapy.

Co-operative randomised prospective clinical trials should be planned in order to assess the utility and the effectiveness of neo- or adjuvant chemotherapy and irradiation in this disease.

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