Introduction

Synovial sarcoma is a highly aggressive and distinct soft tissue sarcoma that, unlike most other soft tissue sarcomas, predominates in young people, causing death in more than 50% of the affected children, adolescents, and young adults. It is a rare tumor, comprising 5% to 10% of all soft tissue sarcomas [1••]. The 5- and 10-year survival rates have been reported as low as 36% and 20%, respectively [2]. Although the diagnostic histologic features for synovial sarcoma are now well defined [3] and its molecular profile is beginning to be elucidated, the clinical pathogenesis of malignancy remains poorly understood. Surgical resection with or without adjuvant radiotherapy and/or doxorubicin-based chemotherapy are the mainstays of treatment. The discovery of the characteristic t(X;18) translocation of synovial sarcoma and the associated fusion proteins has facilitated the diagnosis of synovial sarcoma and led to the investigation of promising new targeted therapies. Because synovial sarcoma remains a very deadly form of cancer, improved therapies are necessary.

Histopathology

Although the name synovial sarcoma connotes a histogenesis from synovium, the characteristic epithelial differentiation of synovial sarcoma is inconsistent with normal synovium. The tissue of origin remains unknown. An alternative name, carcinosarcoma, has been proposed for this histologically biphasic tumor; however, the name synovial sarcoma has been established by convention.

Histologic subtypes

Synovial sarcoma tumors are uniquely composed of two morphologically distinct cell types: spindle cells and epithelioid cells. The
presence of the two cell types in varying proportions lends to the classification of tumors into four histological subtypes that exist along a continuous spectrum: biphasic, monophasic fibrous, rare monophasic epithelial, and poorly differentiated. The biphasic tumor consists of spindle cells and epithelial-type cells in roughly equal proportions.

Light microscopy reveals the spindle cell component to be comprised of small, uniform, and ovoid cells. The nuclei are pale, often with inconspicuous nucleoli. The cytoplasm is sparse, and vague cell borders lend to the appearance of overlapping nuclei. Monophasic fibrous-type tumors demonstrate predominantly spindle cells, with no or minimal evidence of epithelioid differentiation (Fig. 1). These spindle cells are packed into dense sheets with the occasional appearance of palisading nuclei. The tumor stroma involves scant collagen and occasional dense fibrosis, as well as variable mast cell abundance, microcyst formation, and myxoid changes.

Biphasic tumors contain a mélange of spindle and epithelial cell components (Fig. 2). The epithelial component reveals cells with similarly ovoid nuclei but that demonstrate abundant cytoplasm. These cells often form glandular structures with lumina containing epithelial mucin, or papillary structures that resemble adenocarcinoma. The rare monophasic epithelial type is histologically indistinguishable from adenocarcinoma, and cytogenetic analysis is relied on to diagnose synovial sarcoma.

The poorly differentiated type of synovial sarcoma demonstrates common features of high-grade small round cell tumors: dense cellularity, numerous mitotic figures, and areas of necrosis.

**Immunohistochemistry**  
Synovial sarcomas consistently stain positive for cytokeratin and epithelial membrane antigen [3]. Ninety percent of tumors are cytokeratin-positive, with stronger presence in epithelial component than among spindle cells. Occasionally, cytokeratin antigens are expressed in monophasic fibrous–type synovial sarcoma. Unlike other spindle cell sarcomas, synovial sarcomas express cytokeratins 7 and 19, which helps to distinguish synovial sarcoma from malignant peripheral nerve sheath tumors. Epithelial membrane antigens [4] are more commonly present in poorly differentiated–type tumors than is cytokeratin [5]. Because cytokeratin and epithelial membrane antigen do not have perfect overlap, both are used to detect epithelial differentiation in synovial sarcoma.

**Molecular cytogenetics**  
More than 90% of synovial sarcomas demonstrate a specific translocation t(X;18)(p11.2;q11.2) [6]. The breakpoint-associated genes were recently isolated: SYT, on chromosome 18, and SSX1 and SSX2, both on the X chromosome [7]. This discovery led to the isolation of SYT-SSX fusion transcripts. The SYT and SSX proteins localize to the nucleus, where they appear to play a role in transcriptional regulation, SYT as an activator of transcription and the SSX proteins as transcriptional repressors. SYT interacts and colocalizes in the nucleus with the BRM protein, a transcriptional coactivator. The SSX proteins colocalize in the nucleus with polycomb group proteins, which are transcriptional corepressors.

Fusion gene SYT/SSX mRNA can be detected using real-time polymerase chain reaction or fluorescent in situ hybridization (FISH) with frozen or paraffin-embedded tissue. These techniques are particularly useful in identifying monophasic fibrous or poorly differentiated synovial sarcomas that do not have characteristic histological or immunohistochemical diagnoses.

A proposed correlation exists between DNA breakpoint and histologic subtype of synovial sarcoma, with SYT-SSX1 fusion protein being correlated with a biphasic subtype and demonstrating a higher Ki-67 index, or higher mitotic rate, than SYT-SSX2 protein, which is associated with the monophasic spindle cell subtype [7–9]. Cytogenetic data determining tumor karyotype and translocation subtype have also been proposed to have clinical and prognostic significance [6], and extensive research is being performed to determine the extent and validity of tumor cytogenetics, tumor biology, and prognosis [10–15].

**PROGNOSIS**

Data regarding the 5-year survival rates for synovial sarcoma vary significantly, ranging from 36% to 76% [16***]. Favorable prognostic indicators include age younger than 15 years at time of diagnosis, tumor size smaller than 5 cm, and location in the distal extremity [1••, 17, 18]. In a prospective series of 112 patients with synovial sarcoma, tumor size 5 cm or more and presence of bone and neurovascular invasion were found to be independent adverse predictors of distant recurrence and mortality [19].

No clear prognostic correlation has been demonstrated between the histologic subtype of synovial sarcoma and survival. Early analyses indicated that monophasic subtype (associated with the SYT-SSX2 fusion type) had poorer prognosis than did biphasic or SYT-SSX1 subtypes [20]; however, more recent analyses have not corroborated these findings [12]. Heavily calcified tumors have been proposed as having favorable outcomes, with 5-year survival reported to be as high as 82% [3]. Tumors comprised by at least 20% of poorly differentiated pattern have shown to have a worse prognosis [3].

In a retrospective review of 135 patients with synovial sarcoma, those presenting with localized tumors less than 5 cm in longest diameter had a survival at 10 years of 88%, compared with 38% for those with tumors 5 to 10 cm and 8% for patients with