Impact of SYT-SSX Fusion Type on the Clinical Behavior of Synovial Sarcoma: A Multi-Institutional Retrospective Study of 243 Patients


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ABSTRACT

Synovial sarcomas are aggressive spindle cell sarcomas containing in some cases areas of epithelial differentiation. They consistently show a specific t(X;18;p11;q11), which usually represents either of two gene fusions, SYT-SSX1 or SYT-SSX2, encoding putative transcriptional proteins differing at 13 amino acid positions. Previous studies have suggested that patients with SYT-SSX2 tumors do better than those with SYT-SSX1 tumors, but the study groups were too limited to be conclusive. To address this issue more definitively, we collected data on SYT-SSX fusion type, pathology, and clinical course in a retrospective multi-institutional study of 243 patients (age range, 6–82) with synovial sarcoma. SYT-SSX1 and SYT-SSX2 fusions were detected in 147 tumors (61%) and 91 tumors (37%), respectively. Histologically, 61 (25%) were classified as biphasic type and 180 (74%) as monophasic type based on the presence or absence of areas of glandular epithelial differentiation, respectively. Median and 5-year overall survivals for the SYT-SSX1 and SYT-SSX2 groups were 6.1 years and 53%, and 13.7 years and 73%, respectively. Overall survival was significantly better among SYT-SSX2 cases (P = 0.03), among cases localized at diagnosis (P < 0.0001), and among patients with primary tumors < 5 cm in greatest dimension (P = 0.01). Age, sex, histological type, and peripheral primary site had no impact on overall survival. The impact of fusion on type of survival remained significant when stratified for primary tumor size (P = 0.03) but was no longer significant when stratified for disease status at presentation. This may reflect the tendency for patients with SYT-SSX1 tumors to present more often with metastatic disease (P = 0.05). Cox regression identified disease status (P < 0.0001) and primary tumor size (P = 0.04) as the only factors independently predictive of overall survival in the subset of 160 patients with information on all of the factors. Within the subset of patients with localized disease at diagnosis (n = 202), the median and 5-year survival for the SYT-SSX1 and the SYT-SSX2 groups were 9.2 years and 61% versus 13.7 years and 77%, respectively. Patients whose tumors contained the SYT-SSX2 fusion (P = 0.08) were smaller (P = 0.12) showed a trend toward better survival by log-rank test, whereas tumor histology had no impact (P = 0.8). In a Cox regression analysis considering all of the factors, SYT-SSX fusion type emerged as the only independent significant factor (P = 0.04) for overall survival within the subset of 133 patients with localized disease at diagnosis who had information on all of the factors. Among other comparisons, there was a strong association of fusion type and morphology (P < 0.001), with almost all of the SYT-SSX2 tumors showing absence of glandular differentiation (monophasic histology) and almost all of the biphasic tumors containing SYT-SSX1. There was also a statistically significant association of fusion type and patient sex (P = 0.03); specifically, the male:female ratio of SYT-SSX1 cases was 1:1, whereas for SYT-SSX2 cases, it was close to 1:2. Overall, SYT-SSX fusion type appears to be the single most significant prognostic factor by multivariate analysis in patients with localized disease at diagnosis. SYT-SSX fusion type also appears to exert part of its impact on prognosis before presentation through its association with stage at diagnosis. In addition, the associations of SYT-SSX fusion type with patient sex and tumor epithelial differentiation point to interesting mechanistic biological differences.

INTRODUCTION

Synovial sarcomas represent ~10% of all soft tissue sarcomas. More than a quarter of patients succumb to this cancer in the first 5 years after diagnosis despite the best currently available management (1). Histologically, these are spindle cell tumors that are divided into two major subtypes, biphasic and monophasic, according to the respective presence or absence of a well-developed glandular epithelial component. Synovial sarcomas contain in essentially all of the cases a t(X;18;p11;q11) representing the fusion of SYT (at Xq11) with either SSX1 or SSX2 (both at Xp11), or rarely, with SSX4 (also at Xp11; reviewed in Refs. 2, 3; Fig. 1). Neither SYT nor the SSX proteins contain DNA-binding domains. Instead, they appear to be transcriptional regulators of which the actions are mediated primarily through protein-protein interactions. The SSX1 and SSX2 genes encode 188 amino acid proteins that are highly similar. The COOH-terminal 78 amino acids of SSX proteins included in SYT-SSX differ at 13 residues between SSX1 and SSX2, and these differences are conservative (Fig. 1). The significance of the resulting amino acid differences between SYT-SSX1 and SYT-SSX2 to their putative roles as aberrant chimeric transcriptional proteins are presently unknown. SYT-SSX1 and SYT-SSX2 appear to be mutually exclusive gene fusions in synovial sarcoma, and the fusion type is concordant in primaries and metastases and constant over the course of the disease (4).

Associations between alternative forms of an aberrant transcriptional protein and specific clinical features of the associated cancer, such as age at diagnosis, primary site, proliferative rate, or survival, can be an important clue that minor structural differences may nonetheless be functionally significant. Studies in Ewing’s sarcoma and alveolar rhabdomyosarcoma have established the concept that alternative forms of the specific aberrant transcription factors arising from

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5 M. Ladanyi, unpublished observations.
chroomosomal translocations may have an impact on one or more features of the associated sarcoma (5–7). These different associations additionally support the notion that the fusion proteins encoded by these chromosomal translocations are central to the biology of these sarcomas. Indeed, these clinical-molecular associations have been found, in some cases, to be paralleled by differences in fusion protein function (8) or fusion gene expression mechanisms (9, 10). The initial study of this question in synovial sarcoma showed that, among 39 patients with localized tumors, cases with the SYT-SSX2 fusion had a significantly better metastasis-free survival than cases with SYT-SSX1 (11). The finding of a survival advantage for SYT-SSX2 was also reported in two subsequent studies with patient groups of comparable or smaller size (12, 13). A more recent survival analysis of 51 patients with localized synovial sarcoma also found that cases with the SYT-SSX2 fusion had a significantly better metastasis-free survival at 5 years than cases with SYT-SSX1 (4).

In the present study, we sought to establish more definitively the impact of molecular heterogeneity of the t(X;18) on the clinical course of patients with synovial sarcoma through an analysis of SYT-SSX fusion type, pathology, and clinical course in 243 patients with synovial sarcoma.

MATERIALS AND METHODS

Study Group. Patients were seen and/or their tumors analyzed at the following centers: 94 at MSKCC, 39 at University of Nebraska Medical Center, 36 at Scandinavian Sarcoma Group, 34 at Royal Marsden Hospital/Institute for Cancer Research, 21 at University of Pennsylvania Medical Center. SYT-SSX1 and SYT-SSX2 were distinguished by RT-PCR with specific primers in most cases, and in some cases, by RT-PCR with consensus primers followed by sequencing, restriction digestion, or hybridization with specific oligonucleotide probes, or by FISH using OATL1 and OATL2 probes corresponding respectively to SSX1 and SSX2. Technical details of these different approaches are available in previous publications from our laboratories (11, 14–17). Thirty-two tumors from MSKCC and 26 from University of Nebraska Medical Center were studied using RNA extracted from formalin-fixed paraffin embedded material, as described previously (17). All of the remaining cases were analyzed by RT-PCR or FISH using snap-frozen tumor material. SYT-SSX fusion type is an intrinsic property of the tumor maintained at multiple disease sites and over the course of the disease.3 Hence, the source of tumor sample used for molecular analysis was primary tumor in 151, local recurrence in 33, distant metastases in 29 samples, and unspecified in 30 cases.

Statistical Methods. Associations of SYT-SSX fusion type with other key factors were analyzed using 2-sided Pearson χ² test. Survival rates were estimated using the Kaplan-Meier method. Correlations of SYT-SSX fusion type and other factors to survival were analyzed by the log-rank test. Independent prognostic values of factors were studied using Cox regression when three or more factors were being considered and the stratified log-rank test when there were two factors. For each comparison, the n refers to number of cases with complete data, i.e., n is <243 for most comparisons because of some missing data. Overall survival was selected as the most consistent clinical end point because of objectivity and data availability.

RESULTS

Associations Among Factors (Table 1). SYT-SSX1 and SYT-SSX2 fusions were detected in 147 tumors (61%) and 91 tumors (37%), respectively. Five tumors lacked SYT-SSX fusion type data, because either the SYT-SSX fusion could not be detected (2 cases), was detected but could not be typed because of poor RNA (2 cases), or data were unavailable (1 case). There were 180 (74%) monophasic and 61 (25%) biphasic tumors. The strong association of fusion type and histology observed previously (see “Discussion”) was confirmed in this series (n for analysis = 236; P < 0.001). Tumors containing an SYT-SSX1 fusion transcript were monophasic or biphasic, whereas all but three tumors with the SYT-SSX2 fusion were monophasic. Pathological review suggested that gland formation in these three SYT-SSX2 cases was focal and poorly developed compared with the more widespread and well-formed glandular areas in SYT-SSX1 biphasic tumors. There was a significant association of fusion type and patient sex...
Survival Analysis (Patients with Nonmetastatic Disease at Diagnosis; Table 2). Within the subset of patients with localized disease at diagnosis and adequate survival data (n = 202), the median and 5-year survival for the SYT-SSX1 and the SYT-SSX2 groups were 9.2 years and 61% versus 13.7 years and 77%, respectively. Patients whose tumors contained the SYT-SSX2 fusion (n for analysis = 202; P = 0.08; Fig. 5) and were smaller (n for analysis = 174; P = 0.12) showed a trend toward better survival by log-rank test, whereas tumor histology had no impact (P = 0.8). By Cox regression analysis considering all of the factors, SYT-SSX fusion type emerged as the only independent significant factor (P = 0.04) for overall survival within the subset of 133 patients with localized disease at diagnosis who had information on all of the factors. Because axial versus peripheral primary site had no impact on overall survival, a subset analysis of localized extremity tumors alone was not indicated. Combining prognostic factors, there was a considerable difference between 5-year overall survival among the most favorable subset, i.e., SYT-SSX2 and primary <5 cm (86% 5-year survival), compared with the most unfavorable subset, SYT-SSX1 and primary >5 cm (44% 5-year survival).

DISCUSSION

Classic negative clinical prognostic factors in synovial sarcoma include advanced stage, size >5 cm, and local recurrence. These have been observed consistently in essentially all of the recent studies of adequate size (1, 11, 18–21). In some (18–20) but not all of the studies (1, 21), age over 20 or 25 years has also been shown to be a negative factor. Among histological features, tumor necrosis and poorly differentiated areas are reproducible negative factors (18, 19, 21, 22), whereas the significance of monophasic versus biphasic

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Table 1  Associations between SYT-SSX fusion type and other factors a

<table>
<thead>
<tr>
<th>Factors</th>
<th>SYT-SSX1</th>
<th>SYT-SSX2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>44</td>
<td>27</td>
<td>0.82</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>84</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>56</td>
<td>34</td>
<td>0.52</td>
</tr>
<tr>
<td>≥30</td>
<td>67</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>124</td>
<td>82</td>
<td>0.05</td>
</tr>
<tr>
<td>Metastatic</td>
<td>20</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial</td>
<td>41</td>
<td>36</td>
<td>0.07</td>
</tr>
<tr>
<td>Peripheral</td>
<td>102</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monophasic</td>
<td>89</td>
<td>88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biphasic</td>
<td>56</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>31</td>
<td>0.03</td>
</tr>
<tr>
<td>Female</td>
<td>72</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers total less than 243 because of missing data in some cases. Two-sided Ps calculated using Pearson χ².

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**Table 2  Analysis of factors predicting overall survival in all patients and in patients presenting with localized disease only**

<table>
<thead>
<tr>
<th>Factors</th>
<th>All patients (n = 233) a</th>
<th>Patients with localized tumor (n = 202) a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate P</td>
<td>Multivariate P (n = 160)</td>
</tr>
<tr>
<td>Size: ≥5 cm</td>
<td>0.01</td>
<td>.04</td>
</tr>
<tr>
<td>Age: ≥30</td>
<td>&gt;0.9</td>
<td></td>
</tr>
<tr>
<td>Site: Axial</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Histology: Biphasic</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Sex: Male</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Fusion: SYT-SSX1</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>Stage: Metastatic</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a As described in Table 1.

b Ten patients, including 4 with localized tumor at diagnosis, lacked adequate survival data and were therefore excluded from the survival analysis.
SYT-SSX and Synovial Sarcoma

Histology is notoriously inconsistent among different prognostic analyses (1, 11, 19, 21). Our analysis confirms the significance of stage and size but not that of age or monophasic versus biphasic type. Histological grade, an important factor in the prognosis of other soft tissue sarcomas, is not a factor for synovial sarcomas, which are considered uniformly high grade.

Among biological factors, the most widely studied significant negative factor is mitotic rate (19, 21) and related proliferative markers, such as Ki-67, PCNA, cyclin E, and low p27KIP1 (22–26). Whereas two studies found a statistically significant relation between SYT-SSX1 fusion type and higher tumor cell proliferative activity (12, 13), we could not confirm this finding in a similar larger study (17). In our analysis, proliferative rate in synovial sarcomas seemed to associate more strongly with histological type (monophasic versus biphasic) and sample source (primary versus metastatic). P53 status is another biological factor examined previously in synovial sarcoma. P53 mutations appear to be rare in synovial sarcoma, e.g., ~6% of cases (27, 28), but analyses using aberrant P53 expression as a marker of P53 mutation suggest that this small subset of tumors is highly aggressive (25, 27, 28). The potential role of P53 in progression of synovial sarcoma was highlighted by one well-studied patient in whom P53 inactivation was present in the metastatic tumor but not in the primary (29). Other potential biological markers of poor prognosis identified in isolated studies include elevated insulin-like growth factor-I receptor expression, coexpression of HGF and MET, and aberrant β-catenin expression (22, 30–32).

Considering all of the patients in the present study, the median overall survival for the SYT-SSX2 group was about twice that of the SYT-SSX1 group (13.7 versus 6.1 years), and the 5-year overall survival showed a 20% difference (77% versus 61%). By multivariate analysis, SYT-SSX fusion type was the only independent significant factor (P = 0.04) for overall survival. Kaplan-Meier survival analysis of the 202 patients with localized disease at diagnosis showed that ~20% of patients with either fusion type died within the first 3 years. Thereafter, the survival curves diverged, showing the survival advantage for the SYT-SSX2 group. Because death from synovial sarcoma is almost always attributable to distant metastases (e.g., in the present series, of 83 patients who died of their tumor, only 3 had not developed distant metastases) and most patients with metastatic disease at diagnosis die within 3 years, this pattern of early deaths in patients with localized tumors (regardless of SYT-SSX fusion type) suggests the presence of an unrecognized strong negative factor in ~20% of cases. This strong negative factor could be P53 alteration, known to be associated with rapid progression and death within 3 years (see above) or simply undetected macroscopic metastatic disease at diagnosis (i.e., potentially radiographically detectable). The latter would be consistent with the above-noted trend in the present series for patients with SYT-SSX1 tumors to present more often with clinically evident macrometastatic disease. We hypothesize that the survival difference that emerges in the remaining 80% of patients who survived beyond 3 years may reflect a lower rate or slower growth of micrometastases in the SYT-SSX2 group (i.e., radiographically undetectable metastases at initial diagnosis).

Fig. 3. Overall survival according to SYT-SSX fusion type in all patients, regardless of stage. For this comparison, the univariate P was 0.01, and the multivariate P was 0.04. Note that the survival curves cross at ~13 years.

Fig. 4. Overall survival according to primary tumor size in all patients, regardless of stage. For this comparison, the univariate P was 0.01, and the multivariate P was 0.04. Note that the survival curves cross at ~13 years.

Fig. 5. Overall survival according to SYT-SSX fusion type in patients with localized disease at presentation. For this comparison, the univariate P was 0.08, and the multivariate P = 0.04.
The functional basis for clinical correlates of SYT-SSX fusion types is presently unknown. Present models of SYT-SSX oncogenesis incorporate protein-protein interactions described recently with the BRM activator and the Polycomb group repressors, respectively, by the SYT QPGY domain and by the COOH-terminal SSX-RD (reviewed in Refs. 2, 3). A direct comparison of transformation or transactivation by the two different SYT-SSX fusion proteins has not been performed. The SYT portion of SYT-SSX1 and SYT-SSX2 is identical, so putative functional differences would stem from the SSX component, which consists of SSX-RD and the adjacent so-called SSX divergent domain. The COOH-terminal 78 amino acids of SSX proteins included in SYT-SSX differ at 13 residues between SSX1 and SSX2 (Fig. 1). These differences are nonconservative, but 12 of the divergent residues lie outside of the SSX-RD, arguing against significant differences between the two SSX proteins in terms of their putative interactions with the Polycomb group repressors. The role of the so-called “divergent domain” of the SSX proteins remains presently unknown. Recent studies have also shown direct interaction of SYT with the nuclear protein p300 (33) and the AF10 protein, a fusion partner of MLL in some acute leukemias (34).

The association of fusion type and histology observed previously in our laboratories (11, 12, 17) was maintained in this series (n for analysis = 236; P < 0.001). Of 236 cases with data for both fusion type and histological type, there were only 3 SYT-SSX2 biphasic tumors. Pathological review suggested that gland formation in these cases was focal and poorly developed compared with SYT-SSX1 biphasic tumors. The association of SYT-SSX fusion type and biphasic histology, initially suggested by FISH data (35), has also been upheld in several RT-PCR-based studies from other groups, as tabulated by dos Santos et al. (2) as well as in more recent studies (36). Additional investigation of this consistent association between t(X;18) fusion type and biphasic histology may provide insights into the basic histogenetic process of mesenchymal to epithelial conversion and architectural epithelial differentiation (gland formation). We hypothesize that SYT-SSX1 and SYT-SSX2 may differ in the transcriptional deregulation of one or more key genes involved in mesenchymal to epithelial conversion. This question is now being addressed in high throughput studies of gene expression patterns in synovial sarcomas using cDNA microarrays (37).

The present analysis also revealed a statistically significant association of fusion type and patient sex (P = 0.03), reflecting the finding that the female: male ratio of SYT-SSX2 cases was twice that of SYT-SSX1 cases. That this association has not been noted previously may be attributable to the high statistical variability inherent in previous smaller studies, hampering the demonstration of a subtle difference such as this one. The association of fusion type and sex, while statistically significant, was not strong enough to lead to an indirect association of sex and survival (Table 2). The association of fusion type and patient sex suggests differences in the mechanism of the SSX1 and SSX2 gene rearrangements, possibly linked to differences in X-inactivation at these loci. For instance, if SSX2 escaped X-inactivation but SSX1 did not, this could explain why women are twice as likely as men to have an SSX2 rearrangement in their synovial sarcoma. However, both SSX1 and SSX2 seem to escape X-inactivation (38),7 apparently contradicting this simple hypothesis. We should note that remarkably little work, if any, has been done on somatic translocations involving the X chromosome in relation to X-inactivation.

Among other SSX family members, only SSX4 has been found to also fuse with SYT in two otherwise unremarkable synovial sarcomas (36, 39). Published studies (see Table 1 in Ref. 7)8 suggest that SYT-SSX4 is present in only a very small proportion of synovial sarcomas, perhaps 1–2%. Whereas the possibility that rare cases in the present series may actually have contained SYT-SSX4 rather than SYT-SSX1 or SYT-SSX2 could not be systematically excluded in every case for technical reasons, this was not a significant statistical concern because of the expected rarity of these cases. Nonetheless, the presence of the SYT-SSX4 fusion may explain the two tumors in the present series where an SYT-SSX fusion was tested for but could not be identified.

In summary, SYT-SSX fusion type is a significant prognostic factor for overall survival in patients with synovial sarcoma. It appears to exert part of its impact on prognosis before presentation through its association with disease status at presentation. In patients with localized disease at diagnosis, SYT-SSX fusion type was the only significant prognostic factor in the present multivariate analysis. In addition to these survival differences, the associations of SYT-SSX fusion type with patient sex and the presence of glandular epithelial differentiation point to possible biological differences in the mechanism of the gene rearrangements and the function of the chimeric proteins in specific differentiation programs, respectively.

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