Clinicopathological features, treatment and survival outcomes of synovial sarcoma

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Abstract

Introduction: Synovial sarcoma (SS) is a malignant mesenchymal tumor. It is most common among children and adults. The data on SS from India are scarce. In this study, we analyzed the clinicopathological treatment parameters and survival outcomes of SS patients. **Materials and Methods:** A total of 57 histologically proven SS diagnosed from 2010 to 2016 were retrospectively analyzed. **Results:** The median age was 23 years with a male-to-female ratio of 1.28:1. Localized disease was seen in 44 patients (77%) and 13 patients (23%) had metastasis. The primary sites of involvement such as lower limb, upper limb, thorax, and abdomen were seen in 60%, 28%, 7%, and 5% patients, respectively. Surgery was done in 39 patients and 18 patients had unresectable disease. Adjuvant chemotherapy with doxorubicin-based regimen was given in 30 patients and adjuvant radiotherapy in 21 patients. Palliative chemotherapy with anthracycline-based or gemcitabine-based regimen was used in 17 and 2 patients, respectively. The median event-free survival (EFS) was 30 months with 3 years and EFS rate was 36%; median progression-free survival (PFS) was 11.5 months and 1 year; and PFS rate was 38%. On univariate analysis, resection and performance status were significantly associated with survival. There is no impact of grade and size of the tumor on survival. In metastatic patients, the lung is the most common site. **Conclusion:** SS is the most common soft-tissue sarcoma among adults. Resectability and performance status were impacting the survival.

Key words: Clinicopathological, survival, synovial sarcoma, treatment

Introduction

Synovial sarcoma (SS) is a malignant mesenchymal tumor, categorized under "tumors of uncertain differentiation" as per the World Health Organization,[1] and it predominates among all soft-tissue sarcoma (STS) (excluding bone sarcoma).[2,3] Majority of SSs exhibit pathognomonic translocation (X; 18) (p11.2; q11.2), and transcript subtypes such as SSX1, SSX2, and SSX4 are formed depending on the site of X chromosome fusion.[4] Detection of this translocation had become the gold standard in the diagnosis of SS.[5] There is genomic complexity of signatures in SS and these correlate with the metastatic potential.[6] The optimal therapy of SS is unknown because of its rarity and scant published literature. Majority of the data on SS are from the West, and data from the Indian subcontinent are scarce. It is mostly reported along with other sarcomas. The primary objective of this analysis was to study the clinicopathological features, treatments used, and outcomes in patients with SS.

Materials and Methods

Data from medical records of patients with SS diagnosed between 2010 and 2016 were retrieved. Analysis included demographic and clinicopathological features. For those patients who took treatment, outcome parameters such as event-free survival (EFS) were analyzed. Patients with metastatic disease were analyzed for progression-free survival (PFS).

All patients underwent biopsy, magnetic resonance imaging, and contrast-enhanced computed tomography of the chest as part of staging workup. EFS was defined as the time from date of surgery to the time that recurrence was documented, death, or lost to follow-up. PFS in metastatic disease was defined as the time from start of chemotherapy to the date progression was documented, death due to any cause, or lost to follow-up. Patients who had incomplete treatment details were censored for outcome parameters.

GraphPad Prism software for Windows version 7 was used to plot the Kaplan–Meier curves for EFS and PFS (GraphPad software, La Jolla, CA, USA, www.graphpad.com). Univariate analysis for OS was done by plotting Kaplan–Meier curves, and the log-rank test was used to calculate *P* values. Univariate analysis was done to assess the effect of grade of the tumor, size, performance status, and resection status on EFS.

Results

A total of 57 patients were analyzed. The median age at presentation was 23 years (range, 18–53). Male-to-female ratio was 1.28:1. Median tumor size was 13 cm (range, 3–23 cm). The site of sarcoma was lower limb, upper limb, thorax, and abdomen in 34 patients (60%), 16 patients (28%), 4 patients (7%), and 3 patients (5%), respectively.

Fluorescent *in situ* hybridization for t (X; 18) was done in 13 (23%) patients, and all were positive for translocation. The tumor was Grade 3 in 25 patients (44%), Grade 1 or 2 in 27 patients (47%), and unknown in 5 patients (9%). Demographic and pathological parameters are showed in Table 1.

Treatment details

Of the 57 patients, 44 patients had localized disease (77%) and 13 patients had metastatic disease (23%). Thirty-nine patients underwent resection (68%) and in 18 patients (32%), it was unresectable. Wide local excision was done in 28 patients (72%) and amputation was done in 11 patients (28%). Margin status was negative in 25 patients (64%) and positive in 14 patients (36%).

Of the 39 patients who underwent resection, 30 patients (77%) received adjuvant chemotherapy with anthracycline-based chemotherapy and 21 patients (54%) received adjuvant radiotherapy. Neoadjuvant chemotherapy was given in four patients, of which two patients underwent resection.

Eighteen patients (32%) who had unresectable disease or metastatic disease underwent either palliative

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chemotherapy (11 patients [61%]) or palliative radiotherapy (7 patients [39%]). Treatment details are shown in Table 2.

Metastatic site at the time of diagnosis or progression was documented in 38 patients (67%).The sites of metastases are shown in Table 1.

Factors affecting survival

With a median follow-up of 34 months, the median EFS was 30 months (range, 6–82) with a 3-year EFS rate of 36%. The median PFS was 11.5 months (range, 2–19). The 1-year survival rate was 38%. The median PFS is shown in Figure 1.

On univariate analysis, the strongest predictors for EFS were performance status and resection status (P = <0.0001 and P < 0.0001, respectively). Kaplan–Meier estimates of EFS with respect to performance status and resection status are shown in Figures 2 and 3, respectively. Tumor grade and tumor size (P = 0.5 and 0.8, respectively) had no impact on EFS. Kaplan–Meier estimates of EFS with respect to tumor grade and size are shown in Figures 4 and 5, respectively.

Table 1: Demographic and pathological parameters

Parameter	*n* (%)
Gender	
Male	32 (56)
Female	25 (44)
Disease status	
Localized	44 (77)
Metastatic	13 (23)
Performance status	
0/1	40 (70)
2	17 (30)
Site of the disease	
Extremity	50 (88)
Axial	7 (12)
Tumor size (cm)	
<10	22 (39)
≥10	35 (61)
Grade	
1 or 2	27 (47)
3	25 (44)
Unknown	5 (9)
Histology	
Biphasic	41 (72)
Monophasic	5 (9)
Unknown	11 (19)
Margins	
R0	25 (44)
R1	11 (19)
R2	21 (37)
Fish	
Done	13 (23)
Not done	44 (77)
Site of metastasis	
Lung	30 (79)
Others	8 (21)

Table 2: Treatment details

Parameter	*n* (%)
Resection	
Yes	39 (68)
No	18 (32)
Adjuvant therapy	
Radiation	21 (54)
Chemotherapy	30 (77)
Palliative chemotherapy	19
Ifosfamide + doxorubicin	11
Single-agent doxorubicin	6
Gem + doce	2

Discussion

STS is a heterogeneous group of disease with various histological groups, of which SS predominate.[2,3] SS is pathologically differentiated into monophasic and biphasic types depending on cellular differentiation, and nearly all cases exhibit t(X; 18) translocation. A study by Ladanyi showed that 100% of biphasic and 96% of monophasic variants exhibit translocation[5] and subtranscript variants may have prognostic significance.[7] In the present study, only 23% had translocation analyzed mostly due to financial reasons.

The published Indian literature on SS is scarce. A study by Ramaswamy *et al.* on bone and STSs showed that SS was the most common STS.[2] Iqbal *et al.* concluded that SS is the most common histology followed by leiomyosarcoma among nonbone sarcomas.[3]

The most common age groups affected with SS are 10–35 years. The median age in the present study is consistent with this. Extremity and axial involvement were seen in 88% and 12%, respectively, which were consistent with previous studies.

Sultan *et al.* published their experience with 1268 cases of SS in children and adults.[7] Female sex, nonblack race, size of the tumor (<5 cm), extremity location, and localized disease positively correlated with survival. Adults had inferior survival than children. Ferrari *et al.* analyzed 138 patients of localized SS, and risk stratification based on International rhabdomyosarcoma study is significantly associated with survival.[8] Other parameters such as site, grade, size, and transcript subtype did not impact overall survival. The local recurrence rate was 47% in a study by Ates *et al.*, which is probably due to high margin positivity (31%).[9] The 3-year EFS rate of 38% in their study is comparable to the present study (36%).

Ibal *et al.* studied 119 cases of metastatic STS. Factors negatively affecting overall survival included hemoglobin <10 g/dl, tumor size >10 cm, and single modality

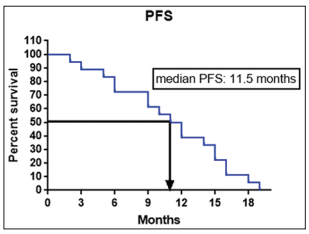

Figure 1: Kaplan–Meier estimates showing progression-free survival

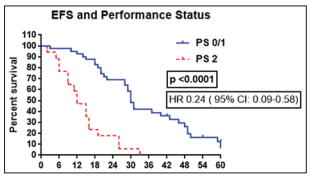

Figure 2: Kaplan–Meier estimates showing effect of performance status on event-free survival

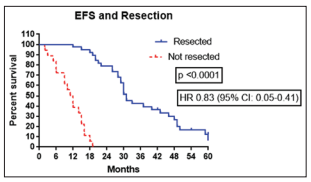

Figure 3: Kaplan–Meier estimates showing effect of resection on event-free survival

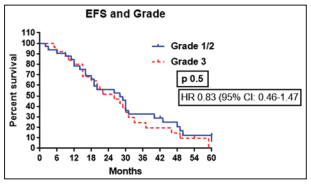

Figure 4: Kaplan–Meier estimates showing effect of grade on event-free survival

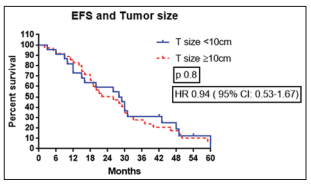

Figure 5: Kaplan–Meier estimates showing effect of tumor size on event-free survival

of therapy.[3] In our study, the most common site of metastasis was lung (79%) followed by lymph nodes (11%) and liver (10%), which were comparable to published studies.[9-12]

Limitations of our study were nonrandomized, retrospective data, and small sample size. However, it reflects the ground reality of treating these patients. Whether SS requires a different treatment approach is currently unknown. Conducting a well-randomized trial exclusively with SS may answer some questions. Drugs targeting SS18-SSX transcript are not available currently, and various pathways such as histone deacetylase,[13] SOX2,[14] Wnt/β-catenin,[14] and mammalian target of rapamycin/AKT[15] inhibitors are candidates for future therapies.

Conclusion

SS is the most common STS among adolescents and adults. The lung is the most common site of metastasis at the time of disease progression. Performance status and resection had significant impact on survival.

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Conflicts of interest

There are no conflicts of interest.

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