Survival and factors affecting the outcome of synovial sarcoma in children and adolescents single institute experience

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ABSTRACT

Introduction: To check the impact of the clinical and pathologic features at diagnosis and treatment given, on the outcome of synovial sarcoma in children and adolescents.

Methods: Retrospective analysis of patients below 18 years old diagnosed by synovial sarcoma and treated at Children Cancer Hospital Egypt 57,357 (CCHE) between July 2007 and December 2016. We reviewed Clinical characteristics, pathological information, treatment modalities and survival data.

Results: We included thirty one patients with median age at diagnosis was 14.8 years. Initial surgical excision was possible in 10 patients (58.8%) while 5 (29.4%) patients underwent surgical excision after response to preoperative chemotherapy. Two patients had unresectable tumor, showed no response to chemotherapy and received radiotherapy as the only local control therapy. Adjuvant radiotherapy only was given in 2 patients and 5 patients received chemotherapy without local radiotherapy and 10 patients received both modalities. The estimated 5-year overall survival and failure free survival rates for the entire group were 84.4% ± 7.2% and 63.8% ± 9.7% respectively, the 5-year OS and FFS were studied in correlation to age of patient, tumor size, different pathological types, site of the lesion and methods of local control. In patients with tumor size below 5 cm when compared to size more than 5 cm with OS was (100%) in comparison to (79.3 ± 9.3) who underwent complete surgical excision either initial or post chemotherapy as it was 66.7% versus 55.6% for those with gross or microscopic residual (p-value = .38). Also, the 3-year failure free survival was 75% versus 56.3% for those smaller than or equal 5 cm and those larger than 5 cm respectively (p-value = .3).

Conclusion: Increasing number of patients to increase sample size to assess tumor size and complete surgical excision as important prognostic factors as in our study, we found them statistically insignificant. Preoperative chemotherapy can help for delayed excision in patients presented initially with unresectable tumors.

Key Words: Synovial sarcoma, Tumor size, Surgery

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1. INTRODUCTION
Synovial sarcoma (SS) is a malignant soft tissue tumor. They are termed SS because of their histologic resemblance to the synovium, but they rarely involve a synovial structure and are thought to arise from pluripotent mesenchymal cells. Synovial sarcoma (SS) is a rare sarcoma driven by a translocation between SS18 and SSX 1, 2, or 4, with approximately 800 to 1,000 cases a year in the United States. SS accounts for 5%-10% of all soft tissue sarcoma with poor prognosis. It occurs predominantly in the young and the middle-aged with a median (35 years). Despite the existence of histologic grading criteria based on mitotic index and tumor necrosis, most SS are considered high-grade tumors. Tumors are either monophasic (pure sarcomas), biphasic (a combination or epithelioid and sarcomatous components), or poorly differentiated. It usually occurs in the extremities but any location may be affected. Symptoms vary based on tumor location, and a slow-growing painless mass is common. It is aggressive and the development of distant metastasis and subsequent death is therefore common. Less than 10% of patients have detectable metastases at the time of diagnosis. In such cases, the lung is the most common site for metastases. Prognostic factors are tumor stage, tumor size, older age, primary tumor site and initial surgical treatment whether with adequate surgical margins or not. However, the significance of these prognostic factors is not well evaluated. Ninety percent of SS have an identifiable translocation between chromosomes 18 and X that results in the fusion of the SYT gene on chromosome 18 and the SSX-1 or SSX-2 gene on chromosome X. Overall survival of patients with localized disease at first presentation ranges from 57% to 88.2% while patients with metastasis at first diagnosis is quite lower. Due to the rarity of SS, there have been no randomized trials studying the use of chemotherapy in its treatment. The current standard treatment as with other soft tissue sarcomas is wide surgical resection followed by chemotherapy with or without irradiation. Surgery is the basic treatment and obtaining adequate margins is its principle aim. Radiotherapy plays a role in improving local control of the tumor and, then, overall survival while the role of chemotherapy in the treatment of SS remains controversial.

The aim was to evaluate the impact of the clinical and pathologic features at diagnosis and treatment given, on the outcome of synovial sarcoma in children and adolescents.

2. PATIENTS AND METHODS
Retrospective analysis of patients below 18 years old with pathological diagnosis of synovial sarcoma and treated at Children Cancer Hospital Egypt 57,357 (CCHE) between July 2007 and December 2016 with a median follow-up period of 20.8 months (range 3.37-52.8) months.

All patients had the full initial workup including CT imaging or MRI as local assessment of the site involved assessment of metastasis by Chest X-ray, CT chest, and bone scan. Clinical characteristics, pathological information by immunohistochemistry and genetic studies when possible were done, treatment modalities and survival data were recorded and analyzed.

3. PATHOLOGY
3.1 Synovial sarcoma pathological types have been described
In the monophasic type, there is a predominance of spindle cells, mixed with round cells; cells are arranged in fascicles with a poorly defined cytoplasm; no glandular areas are present. The biphasic type has a layer of columnar epithelium in addition to spindle cells; it consists of plump, round cells and spindle-shaped fibroblasts alternating with glandular.

3.2 Immunohistochemistry
Translocation between chromosomes 18 and X that results in the fusion of the SYT gene on chromosome 18 and the SSX-1 or SSX-2 gene on chromosome X were studied.

3.3 Treatment
We treated patients by hospital approved protocol for non-rhabdomyosarcoma soft tissue sarcoma adopted from COG-ARST0332 as shown in Figure 1.

3.4 Statistical analysis
Patients’ data were tabulated and processed using (SPSS) statistical package (20) for Windows. Qualitative data were
expressed as frequency and percentage, while quantitative data were expressed as mean ± SD. Chi-square test and Fisher Exact test were used. Statistically significant level was considered at \( p \leq .05 \).

Survival estimates were calculated using the Kaplan-Meier method. The differences between curves were tested for statistical significance using the log rank test. Patients without the end point events were censored on the date of the last reported contact.

Failure-free survival (FFS) was defined as the time from initial diagnosis to disease progression, recurrence, or death as a first event.

Overall survival (OS) was defined as the time from initial diagnosis to death whatever the cause is.

4. Results

Thirty one patients were diagnosed and treated during the study period Registration date from 7-7-2007 till 31-12-2016 and patients were Followed up till 30-12-2018. Synovial sarcoma patients constituted 5.2% of soft tissue sarcoma patients. Twenty one patients were above 10 years and 10 patients were From 1 year to 10 years. Median age at diagnosis for the study cohort was 12.36 years (range 1-17.6 years) with a mean of 12.27 years. Male: female ratio was 1.7:1. The most common affected primary site was the extremities in 20 cases (64.6%) with Lower limb mainly (14 cases). Eight cases were abdominopelvic (25.8%), 2 cases in chest and one case head and neck.

Initial tumor size was reviewed and five patients had tumor size less than or equals 5 cm (32.3%) and 23 had tumor size more than 5 cm (74.2%) and 3 patients had unknown size: (9.7%).

Pathological types mainly biphasic type in 25 patients and 6 patients were monophasic type. Based on pathological study (immunohistochemistry and genetic study). Genetic analysis was done in 12 cases out of the 31, nine cases were proved to be positive to fusion of the SYT gene on chromosome 18 and 3 cases failed.

Most of the patients were categorized into intermediate risk 27 patients (87.2%) 2 patients of low and 2 patients with high risk.

Regional Lymph nodes were clinically involved in 3 cases, not involved in 22 cases and 6 cases were of unknown status. High risk patients were metastatic initially and both were presented with lung metastasis.

We treated patients according to non Rhabdomyosarcoma protocol based on CHILDREN’S ONCOLOGY GROUP COG (ARST0332) Study. Patients were categorized according the protocol with two Patients (6.7%) had Arm A, 3 patients (10%) had Arm B, 18 patients (56.7%) were on Arm C and 8 patients (26.7%) categorized to Arm D. Twenty cases had only surgery as local control method, 10 cases had both surgery and radiotherapy as local control method and only one had radiotherapy only. Patients who had surgery as local control method 19 cases had initial surgery and 11 cases had delayed surgery. The estimated 5-year overall survival and failure free survival rates for the entire group were 84.4% ± 7.2% and 63.8% ± 9.7% respectively. Twenty two patients were alive, 6 patients were died and 3 patients lost contact. Overall survival and disease free survival were correlated according to age, site of the tumor, method of local control, initial tumor size and pathological types. The 5 years OS to patients above 10 years was 79.3% ± 9.3% in comparison to 100% in patients had age between 1 and 10 years with a \( p \) value (.107) and FFS was 56.9% ± 12% in above 10 years group and 80% ± 12.6% in one to 10 years age group (\( p \) value was .3) (see Figures 1 and 2).

![Image](http://jst.sciedupress.com/JST/V9/I2/ART/08.jpg)

**Figure 2.** FFS of the whole cohort. 3-Years FFS = 48.8% ± 14.8%.

For the 5-year FFS based on tumor size it was 100% versus 55.9% ± 12.1% for those smaller than or equal 5 cm versus those larger than 5 cm, respectively (\( p \)-value=.134) (see Figure 3).

Twenty patients had local control of both surgery and radiotherapy and 10 cases had surgery only. OS and FFS were studied according to method of local control found to be insignificant (see Figure 4).

Patient had initial surgery were 19 cases and patients who did surgery after neoadjuvant chemotherapy were 11 cases. Eleven cases showed recurrence 6 cases had a distant recur-
rence, 3 cases had local recurrence and one case had both and another case showed regional recurrence (see Figure 5).

Figure 3. OS by tumor size. 3-Years-OS for those with tumor size $\leq 5 \text{ cm} = 100\%$, versus $81.5\% \pm 11.9\%$ for those with tumor size $> 5 \text{ cm}$ ($p$-value $= .38$)

Figure 4. FFS by tumor size. 3-Years-FFS for those with tumor size $\leq 5 \text{ cm} = 75\% \pm 21.7\%$, versus $37.5\% \pm 18.2\%$ for those with tumor size $> 5 \text{ cm}$ ($p$-value $= .29$)

5. DISCUSSION

Synovial sarcoma is a clinical, morphological, and genetic well-defined entity that arises from primitive pluripotent mesenchymal cells unrelated to synovial tissue. It is a malignant soft tissue tumor accounting for 5%-10% of all soft tissue sarcomas\[15\] this corresponded to our study it constituted 5.2% of all soft tissue sarcoma.

In this study a retrospective analysis of patients below 18 years old diagnosed by synovial sarcoma and treated at Children Cancer Hospital Egypt 57,357 (CCHE) between July 2007 and May 2016, Seventeen thirty-one patients were included in the study. In the current study median age was 12.36 (min age 1 -max age 17.6) with a mean age = 12.27 years with a male: female = 2.4:1. In literature, it occurs predominantly in the young and the middle aged with median age 5 years.\[8\] In the current study, the most common affected primary site was the extremities 20 cases about 63% of cases. Many studies indicated that synovial sarcoma usually occurs in the extremities but any site may be affected.\[7\] According to Deshmukh et al, the incidence of synovial cell sarcoma has been estimated to be 2.75 per 100,000 and most cases involve the lower extremities.\[9\] Previous studies have been performed to find important prognostic predictors. Results show that a younger age, a smaller tumor size, a distal limb site, and negative resection margins are correlated with improved outcomes. Adjuvant radiation therapy is also correlated with improved outcomes.\[16\] Local control for patients with non-metastatic disease was excellent. The overall cancer-specific survival rate for patients with localized synovial sarcoma was 34% at 10 years.\[17\]

According to Lewis et al, overall survival of patients with localized disease at first presentation range from 57% to 88.2% while patients with metastasis at first diagnosis is quite lower.\[7\]

In the current study the estimated 5–year overall survival and failure free survival rates for the entire group were 84.4% ± 7.2% and 63.8% ± 14.9% respectively. Still its five years survival by increasing follow-up survival rates may be lower.

Figure 5. FFS by Method of local control. 3-Years-FFS for those who underwent surgical excision either initial or post chemotherapy = 51.9%, versus 70.6% for those with both surgery and radiotherapy ($p$-value $= .033$)

In the literature, it was found hat size has a significant effect on metastasis-free, overall, and local recurrence-free.\[16\]
In the current study, the 5-years OS ≤ 5 cm = 100% and 5-years OS > 5 cm = 79.3% ± 9.3 (p-value = .33). The 5-years DFS ≤ 5cm = 100% and 5-years DFS > 5 cm = 55.9% ± 12.1 (p-value = .134). OS and DFS were found to be insignificant may be due to small sample size.

In contrast to Kawai A, et al. 1998 who found that prognosis was associated with tumor size,\(^{[15]}\) but in another study, Bernard M, et al. 2011 did not demonstrate that tumor size has an influence on the outcome of SS (p-value=.107).\(^{[18]}\)

In the current study most of the cases were in extremities the 5-years OS and FFS of non-extremities = 66.7% ± 19.2% and 3-years FFS of lower limb = 92.3% ± 7.4% in contrast to another study, patients with limb-based metastasis-free (p-value = .522) in contrast to another study, patients with limb-based tumors had significantly better overall (p-value = .001) and metastasis-free (p-value = .07).\(^{[18]}\)

As in other soft-tissue sarcomas, the quality of the surgical operation is crucial. Obtaining adequate surgical margins is essential to gain tumor control, and is strongly influenced by the type of healthy tissue surrounding the tumor.\(^{[11,18]}\) This is supported by our results, which showed that patients with a primary wide resection had a better outcome the 3-years FFS for those who underwent complete surgical excision either initial or post chemotherapy 66.7% ± 19.2% and 3-years FFS for those with gross or microscopic residual = 55.6% ± 16.6% (p-value=.38).

6. CONCLUSION

Increasing number of patients to increase sample size to assess tumor size and complete surgical excision as important prognostic factors as in our study they were found to be statistically insignificant. Preoperative chemotherapy can help for delayed excision in patients presented initially with unresectable tumors.

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