Synovial Sarcomas: Insights into Management and Outcomes from a Tertiary Cancer Centre

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Abstract

Aim and Objectives: The aim of this study was to evaluate the management and outcomes of patients with synovial sarcoma in the extremities.

Material and Methods: 46 patients were included in this retrospective longitudinal study conducted at a tertiary cancer center between 2010 and 2017. There were 29 males with a median age of 21 (7-70) years and 17 females with a median age of 35 (13-50) years. On immune-histochemical staining CD-99 and vimentin stained positive in 100%, and BCL2 Positive in 94 %.

Results: Limb salvage with wide excision was performed in 28 (61%) and amputation was needed in 18(39 %).12 (26%) received neoadjuvant chemotherapy with ifosfamide and Adriamycin-based chemotherapy. Older Age (>25 years) was associated with lower 5-yeardisease-free survival (p=0.04). The high-grade tumor was associated with lower 5-year disease-free survival (p=0.008). The 5-year disease-free survival in tumor size ≤ 10 cm compared to tumor size >10 cm had no significant difference. The median disease-free survival in the neoadjuvant chemotherapy group as compared to no neoadjuvant chemotherapy was (28.5 vs 21 months) (p>0.05). The adjuvant treatment group and non-adjuvant treatment group had median disease-free survival of 29 months and 11.5 months respectively.

Conclusion: The age of the patient, stage of the tumor, tumor differentiation, and metastatic disease at presentation are risk factors for poor survival for patients with synovial sarcoma. The patients treated with adjuvant radiotherapy or adjuvant chemoradiation had beneficial outcomes as compared to patients who received no adjuvant treatment.

Keywords: Synovial Sarcoma, Extremities, Outcomes, Immunohistochemical study (IHC)

1. INTRODUCTION

Synovial sarcoma (SS) is a high-grade soft tissue sarcoma characterized by a variable degree of spindle and epithelial cell differentiation [1–4]. The chromosomal translocation involves three variants of SSX (SSX1, SSX2, and SSX4) fused to the SYT gene (SS18) [5–8]. The biphasic tumor contains both spindle- and epithelial-like cells that tend to have the *SYT*-SSX1

fusion, whereas the monophasic tumor contains only spindle cells that tend to have *SYT-SSX2* fusion. It is a distinct soft tissue sarcoma, occurring across all ages, from young children to the elderly, but the incidence of SS peaks in young adults. It occurs most frequently in the lower extremities, while it is less common in the upper extremities, head, neck, and trunk [1, 9]. For resectable early-stage disease, the mainstay of the treatment approach is surgical resection, followed by adjuvant radiation with or without adjuvant chemotherapy [10]. In patients with locally-advanced tumors invading critical surrounding structures such as vessels or nerves, pre-operative radiation and/or chemotherapy may be used to downstage the disease first, followed by surgical resection. Tumor size, margin status, histological grade, age, sex, and bone and vascular invasion have been shown to be associated with outcomes, with larger tumor size (>5.0 cm) being consistently shown to be associated with shorter disease-free survival (DFS) and overall survival (OS)[11,12-16]. The aim of this study was to evaluate the management and outcomes of patients with synovial sarcoma in the extremity.

2. MATERIAL AND METHODS

46 patients were included in this retrospective longitudinal study conducted at a tertiary cancer center between 2010 and 2017. The diagnosis in all cases was confirmed by tissue biopsy and immunohistochemistry. Follow-up data was collected till May 2018. Magnetic resonance imaging (MRI) was routinely performed for the initial assessment of the primary tumor and Contrast-enhanced computed tomographic scan (CECT) thorax, abdomen, and pelvis to rule out metastatic disease. Follow-up surveillance was done by history and physical examination, USG or MRI local part as indicated and CECT thorax every 3-6 months. We had 53 patients treated with synovial sarcoma and included 46 patients for the current study and excluded 7 patients due to lack of follow-up data.

Patients with a lack of follow-up data were excluded from the study. 29 were male with a median age of 21 (7-70) years and 17 were female with a median age of 35 (13-50) years. The most common site for the disease was the lower extremity followed by the upper extremity and in the lower extremity, the most common site was the thigh (Table 1). Of the total 46 patients included in the present analysis, immune-histochemical staining was performed in 39 patients. On histological subtyping 41.3% (19/46) were monophasic, 23.9% (11/46) were biphasic, 23.9% (11/46) were poorly differentiated and in 10.9% (5/46) histological subtyping was not performed. On immunohistochemical staining CD-99 and Vimentin stained positive in 100% of cases, BCL2 Positive in 94.6% of cases and Desmin stained negative in 100% (Table 2). 42 patients were nonmetastatic and 4 patients were metastatic at the time of presentation. All the patients with metastatic disease at the time of production had lung metastasis and primary tumor size > 5.0 cm with poor differentiation on histology. At presentation, 30.4% of patients were stage I, 13% were stage II, 47.9% were stage III, and 8.7% were stage IV disease

Factors affecting survival were analyzed using Kaplan-Meier survival curve. Log Rank (Mantel–Cox) test was used for survival outcomes. Median survival was calculated using a survival curve comparing the two groups. All calculations were performed using Statistical Product and Service Solutions (SPSS, version 17).

3. RESULTS

Limb salvage with wide excision of the tumor was performed in 60.86% (28/46) of patients while major amputation was performed in 39.14% (18/46) patients. 43 (94%) had negative surgical margins and 3(7%) had a microscopic positive margin. 41.3% (19/46) of patients had

relapses out of which 17 in only pulmonary metastases and two patients had local recurrence and pulmonary metastases. The median time to relapse after surgery was 14 months. In two patients pulmonary metastasectomy was performed but both patients developed a second relapse in the lung within three months. 12 (26%) patients were given neoadjuvant chemotherapy and none of them received preoperative radiation. Patients who received NACT had either a close relation to the neurovascular bundle or a possibility of a close surgical margin. Nine patients received ifosfamide and Adriamycin-based chemotherapy, one patient received Adriamycin single agent and two patients received VAC protocol. Pre-NACT Average tumor size was 9.7 cm and 10.04 cm post-NACT. 65.2% (30/46) of patients received adjuvant treatment. 41.2% (19/46) patients were given PORT only while 24% (11/46) patients received post-op chemoradiation, and no standard protocol for adjuvant treatment was established. On final evaluation, 50% (23/46) of patients were alive and disease free, 17.4% (8/46) were alive with metastatic disease, 32.6% (15/46) patients died of disease and the most common cause of death was relapsed in the lung.

There was no statistically significant difference in 1, 3, and 5-year survival between the two sexes. 47.8% (22/46) patients were aged ≤25 years and 52.2% (24/46) patients were aged >25 years in the present study (Figure 1). There were, however, significant differences ($P<0.05$) in the 3 and 5-year DFS(Disease free survival) and OS(Overall survival) rates between those patients aged 0–25 years and those patients aged >25 years, (DFS - 40.9% vs 12.5% and 9.1% vs 4.2%) & (OS – 63.6% vs 29% and 36.4% vs 8.3%) respectively, however, there was no significant difference in 1 year DFS and OS(Table 3,4).

The median DFS of stage I, II, and III disease were 37.5, 24.5, and 20 months respectively and the median Overall survival of stage I, II, III, and IV disease were 45, 31, 24, and 8.5 months respectively. The 1, 3, and 5-year DFS and OS are also higher in early-stage disease as compared to advanced disease which is statistically significant(Figure 2). Tumor grade also had a significant impact on DFS and OS(Figure 3). The median DFS and OS in the well-differentiated tumor were 37.5 and 45 months while in the poorly differentiated tumor were 19 and 23.5 months which was statistically significant ($p<0.05$). The three and five-year DFS and OS was also significantly higher in the well-differentiated tumor as compared to the poorly differentiated tumor ($p <0.05$) (Table 3,4) while one-year DFS and OS were comparable in both groups. Patients with the nonmetastatic disease had significantly higher OS as compared to those with metastatic disease ($P = 0.00$). In the present study tumor size ≤ 10 cm was compared to tumor size >10 cm and no significant difference in 1, 3 and 5 year DFS and OS in the two groups were found(Table 3,4). The median DFS and OS in the Neoadjuvant chemotherapy (NACT) vs No NACT group was (28.5 vs 21) and (37.5 vs 24) months which shows a trend towards improved DFS and OS in the NACT group but it was not statistically significant.1, 3, and 5-year DFS and OS also showed a trend towards improvement but it was not statistically significant ($p>0.05$) (Table 3,4)(Figure 4).

Patients who had been given adjuvant treatment had improved median DFS and OS at 29 and 37 months, as compared to those without adjuvant treatment at 11.5 and 29 months. The 1, 3 and 5-year DFS in the adjuvant treatment group is also improved as compared to the no adjuvant treatment group which was statistically significant (p-value 0.03,0.02, and 0.04 respectively)(Figure 5). 1-year OS is also improved but it was not statistically significant ($P= 0.07$), while 3 and 5 years OS was statistically significant in the adjuvant treatment group (P value of 0.03 and 0.05)

4. DISCUSSION

Soft tissue sarcomas are a group of tumors that arise in the connective tissues throughout the body. They account for approximately 1% of adult malignancies and 5 to 15% of pediatric malignancies [1-5]. Synovial sarcoma presents with a mass or swelling over the extremity and biopsy with immunohistochemical staining with a variable set of markers is used for diagnosis [17-18]. In a study by Pan et al 100% of the cases stained positive for BCL2, and 90% of cases stained positive for CD99, similar results were also seen in studies published by Mancuso et al and Hirakawa et al [38, 19, 20]. In the present study on immunohistochemical staining of CD-99 and Vimentin stained was positive in 100% of cases, BCL2 Positive in 94.6% of cases and Desmin stained negative in 100%.

Several clinical factors have been studied to characterize their impact on prognosis and survival [21-31,38]. In a non-randomized study of pediatric patients with synovial sarcoma, patients were grouped into low, intermediate, and high-risk based on tumor size and respectability [25]. Twenty-six patients in the low-risk category with tumor size < 5.0 cm who were treated with surgery alone had 5-year event-free survival (EFS) at approximately 80% and OS at 90%, while 67 patients with high-risk features (larger Unresectable tumor, axial primary, or with nodal involvement) had much worse EFS(Event free survival) and OS [25]. Tumor size and primary tumor location have been shown to be significantly associated with DFS in several other studies [11,12, 26-28]. In a study by Pan et al 130 cases of early-stage synovial sarcoma showed that tumor size > 5.0 cm was associated with approximately three-fold worse DFS, sarcoma-specific mortality, and all-cause mortality [38]. 23 cases in this cohort who presented with stage IV had a poor OS of 1.3 years. [38]. Tumor location at the distal or proximal region of the extremity may be associated with a difference in OS [12,14,28].

In the present study 65.2% (30/46) patients had tumor size ≤ 10cm and 34.8% (16/46) patients had tumor size >10 cm, however, we found no significant difference in median and 1.5-year DFS and OS. Metastatic disease at presentation in the present study had significantly poor median and 1,3,5 years OS. Median OS in metastatic and nonmetastatic disease was 8.5 vs 34 months (P=0.00).

Studies by Ferrari et al the benefit of pre-and post-operative chemotherapy for STS havea led to intense debate over the last two decades [25, 31]. There is no randomized clinical trial of pre- or post-operative chemotherapy specifically for synovial sarcoma. Only one randomized prospective trial, conducted by the Italian Sarcoma Group (ISG), showed OS advantage with adjuvant chemotherapy using epirubicin and ifosfamide in patients with extremity and girdle high-grade STS [32]. Other trials (mainly two large EORTC trials) have largely failed to demonstrate the benefit of adjuvant chemotherapy although the meta-analyses have shown modest OS benefit [33-37]. A retrospective study of more than 300 cases of synovial sarcoma by Canter et al. with a pre-operative nomogram predicted an early survival benefit with ifosfamide and Adriamycin-based chemotherapy [11]. A retrospective study by Pan et al received pre-and/or post-operative chemotherapy and showed no improvement in either DFS or OS [38].

In the present study, 12 (26%) patients received neoadjuvant chemotherapy. Nine patients received ifosfamide and Adriamycin-based chemotherapy, one patient received Adriamycin single agent and two patients received VAC protocol. No significant difference in MRI tumor size in pre and post-NACT. The median DFS and OS in NACT vs NO NACT group was (28.5 vs 21) and (37.5 vs 24) months which shows a trend towards improved DFS and OS in the NACT group but it was not statistically significant. 1, 3, and 5-year DFS and OS also showed a trend towards improvement but was not statistically significant (p>0.05)

In the present study, 65.2% of patients received adjuvant treatment. 41.2% of patients were given PORT and 24% of patients received post-op chemoradiation. Patients who had been given adjuvant treatment had improved median and 1, 3, and 5-year DFS and OS. However, given its retrospective nature, the data can only be suggestive, not conclusive. A randomized chemotherapy trial specifically for synovial sarcoma in a neoadjuvant or adjuvant setting would be of great significance.

The question about the benefit of metastasectomy remains inconclusive [30]. Pan et al. found that 13 of 26 patients who relapsed with predominantly lung metastasis received metastasectomy and had an OS of 7.8 years, compared to 2.3 years of patients who did not receive metastasectomy [38]. In a study by Kang et al of 29 patients who received metastasectomy, five-year OS was 58.4% [39]. In a study of pediatric patients by Stanelle et al with synovial sarcoma (<22 years old), there was a suggestion of improved OS with metastasectomy [28]. However, the improved OS for patients who underwent metastasectomy could be due to their disease burden being more limited, rather than the procedure itself. In the present study, 17 patients had a relapse in the lung only, in two patients lung metastasectomy was performed but both patients developed a second relapse in the lung within three months. The five-year survival rate of synovial sarcoma ranges from 37% to 90% in the published literature [21-24]. In the present study, the five years overall survival is 21.7% which was less as compared to the previous studies. This low overall survival rate may be due to the advanced stage of disease at presentation in this region.

The limitations of our study include that it is a retrospective study. The majority of patients who received chemotherapy were given doxorubicin and an ifosfamide-based regimen. Also, the majority of patients who received radiation also have relatively constant doses between 45-50 Gray. A randomized chemotherapy trial specifically for synovial sarcoma in a neoadjuvant or adjuvant setting would be of great significance.

5. CONCLUSION

The age of the patient, stage of the tumor, tumor differentiation, and metastatic disease at presentation are risk factors for poor survival for patients with synovial sarcoma. The patients treated with adjuvant radiotherapy or adjuvant chemoradiation had beneficial outcomes as compared to patients who received no adjuvant treatment.

Legends of Figures
Figure 1: Kaplan –Meier survival estimates for Age-related survival
Figure 2: Kaplan –Meier survival estimates for Stage related survival
Figure 3: Kaplan –Meier survival estimates for Grade related survival
Figure 4: Kaplan –Meier survival estimates for the Neoadjuvant chemotherapy (NACT) group vs No NACT Group related survival
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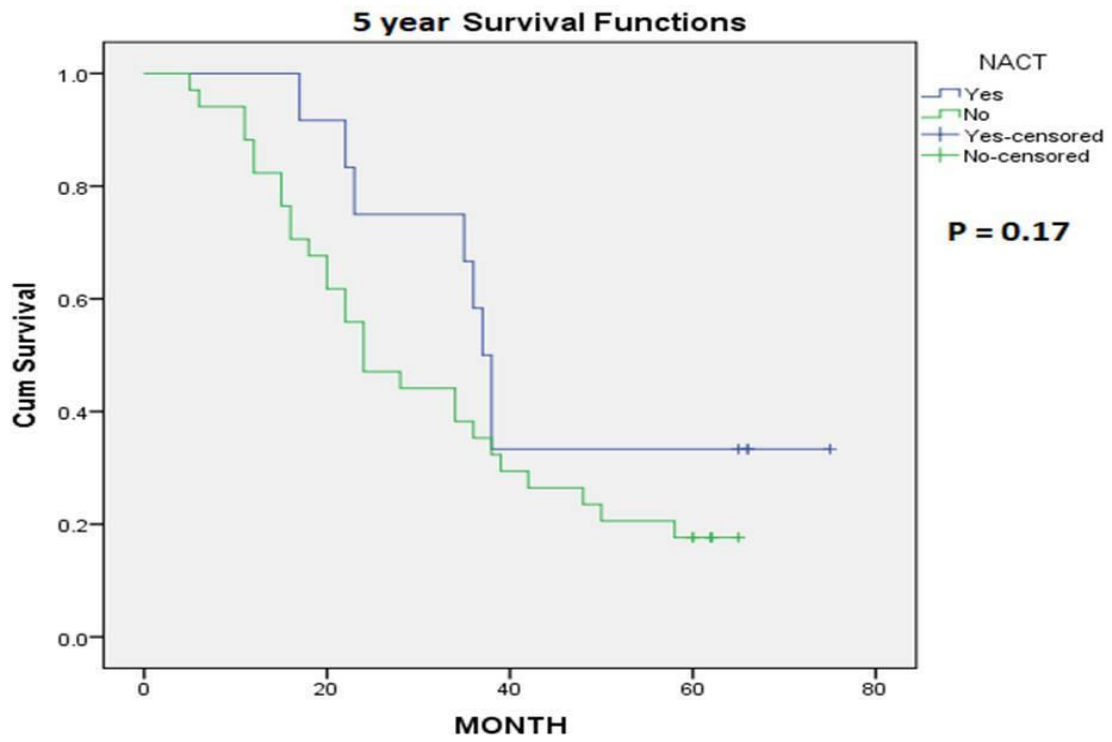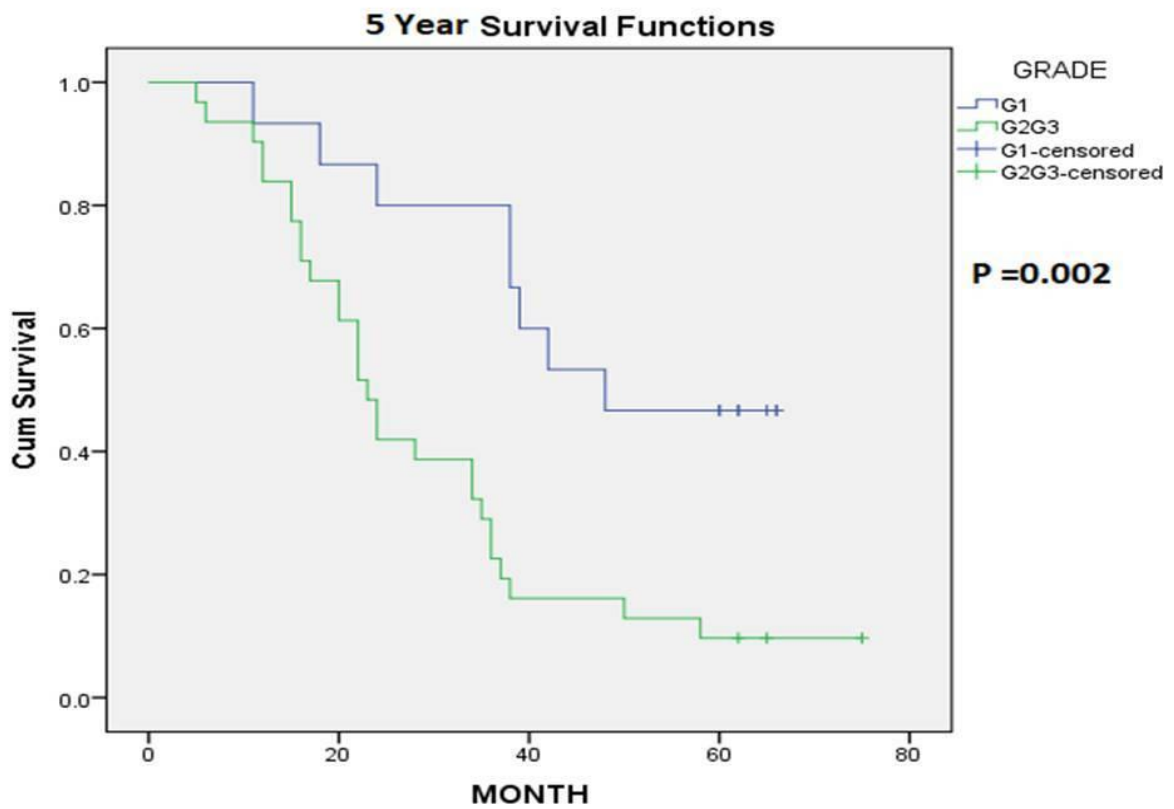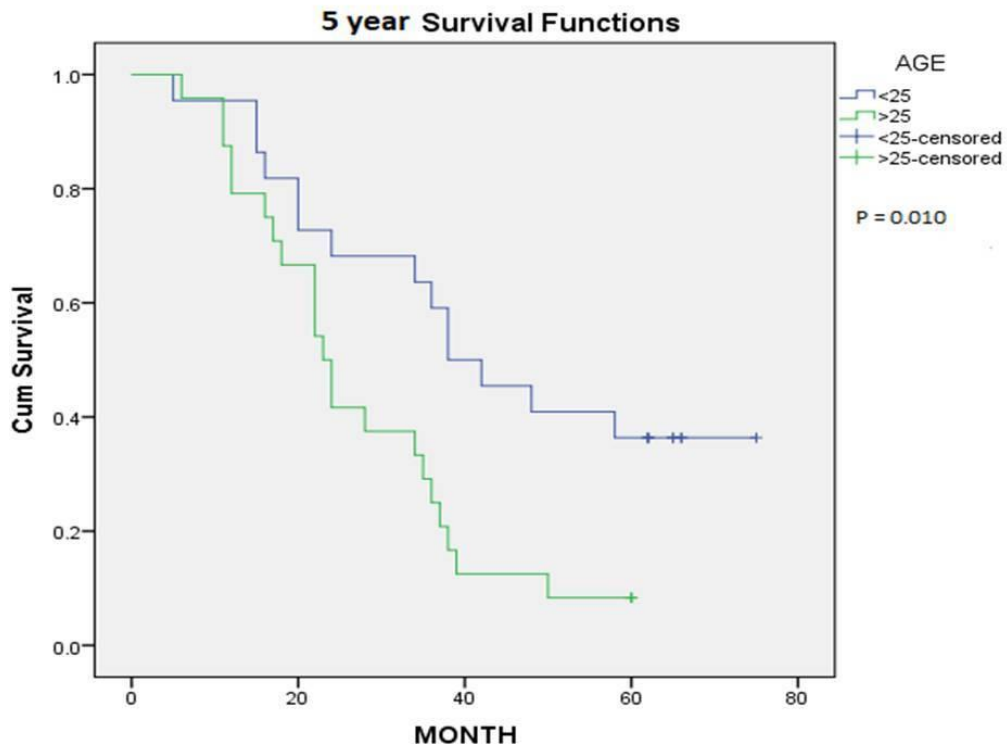
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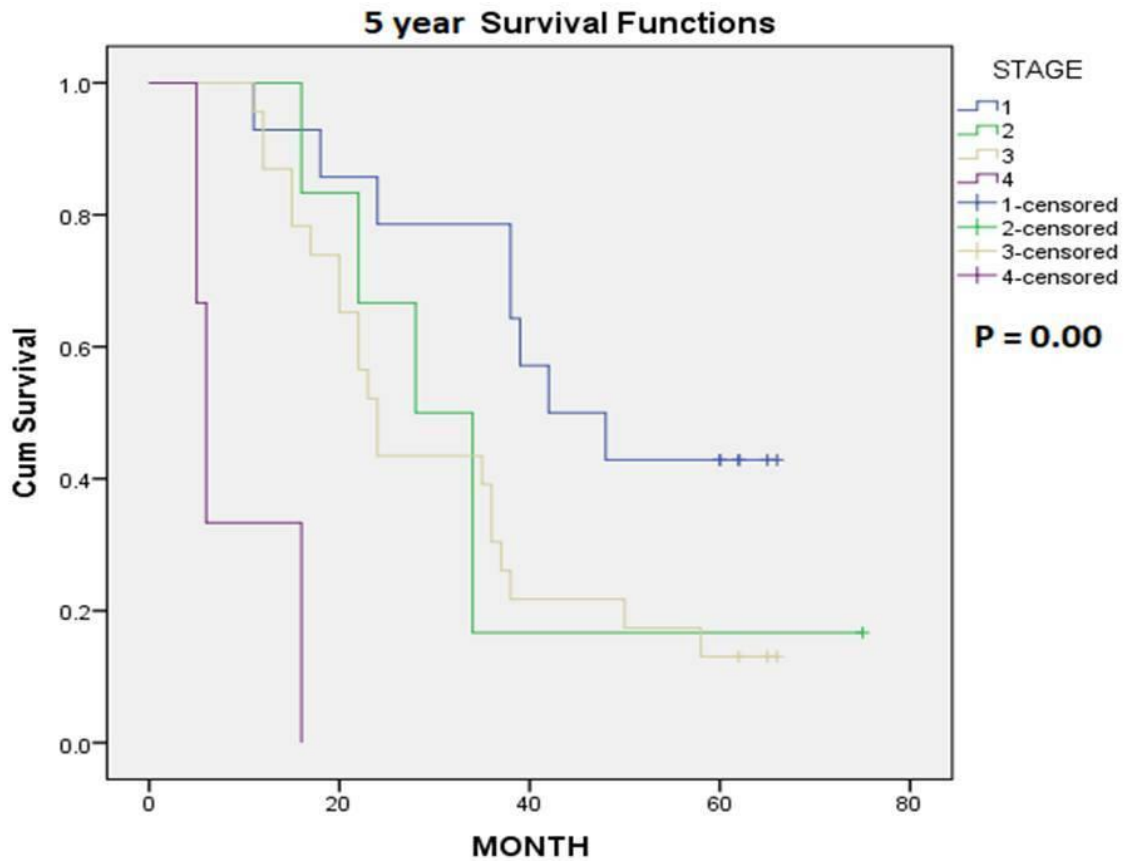
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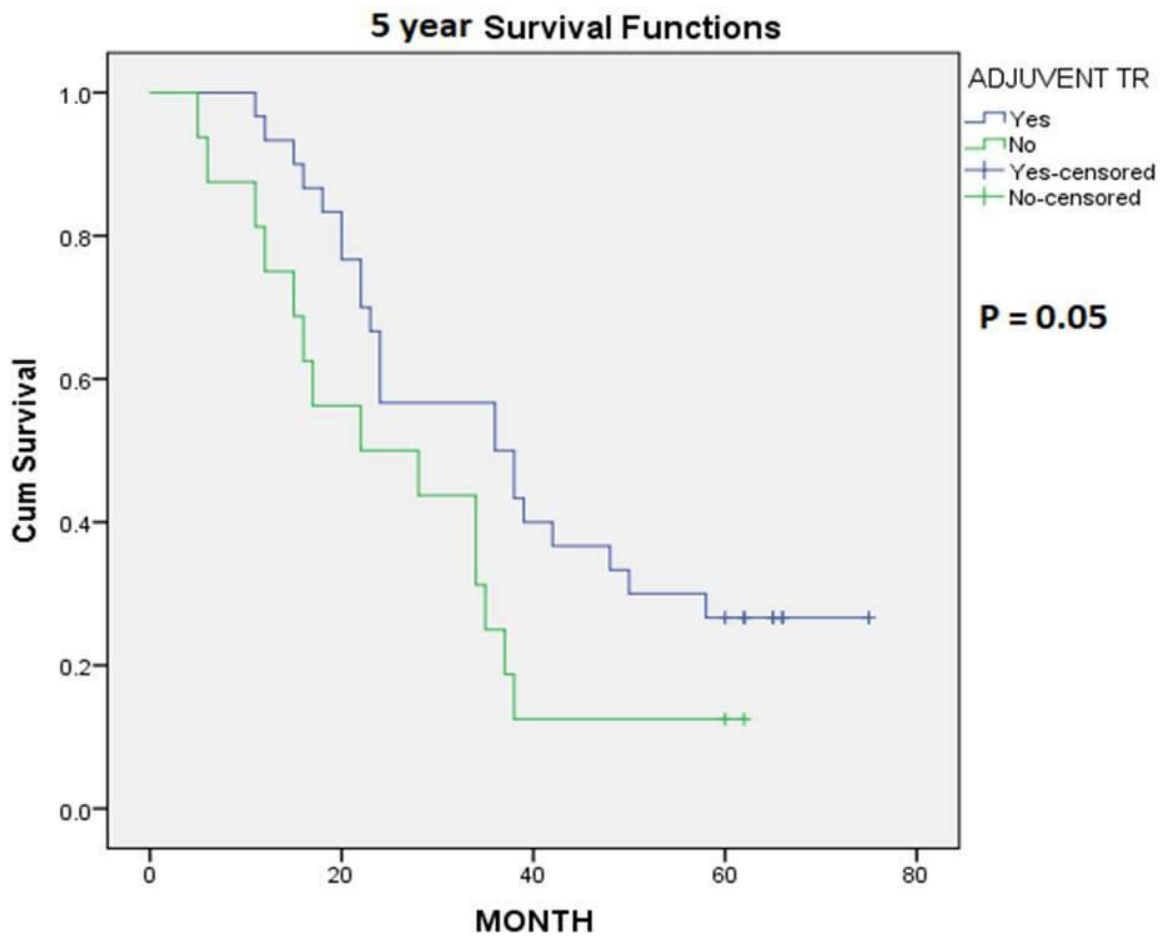
Table 1: Site-wise distribution of Synovial Sarcoma

UPPER EXTREMITY (14)	LOWER EXTREMITY (32)
Elbow = 1	Foot = 5
Hand = 5	Ankle = 1
Wrist = 3	Leg= 3
Forearm = 3	Knee = 3
Arm = 2	Thigh = 18
	Gluteal = 2

Table 2:-Immuno-histochemical (IHC) staining characteristics in patients with Synovial Sarcoma Cases

VARIABLES	IMPACT ON 1 YR OS		IMPACT ON 3 YR OS		IMPACT ON 5 YR OS	
	Chi square	P value	Chi square	P value	Chi square	P value
AGE(≤25 year vs >25 year)	**0.82**	**0.365**	**4.65**	**0.03**	**6.66**	**0.01**
GENDER(Male vs Female)	**0.29**	**0.59**	**0.04**	**0.82**	**0.005**	**0.94**
TUMOR SIZE ON MRI(≤10cm vs >10 cm)	**0.42**	**0.51**	**0.34**	**0.55**	**0.13**	**0.71**
STAGE	**23.43**	**0.00**	**30.55**	**0.00**	**30.52**	**0.00**

Table 3: Impact of different variables on 1, 3 and 5 year overall survival on univariate analysis

IHC MARKER	POSITIVE	NEGATIVE	% POSITIVE
BCL -2	35	2	94.6%
CD – 99	24	0	100%
VIMENTIN	36	0	100%
FLI1	2	0	100%
EMA	17	7	70.8%
CK7	3	2	60%
AE1	14	7	66.7%
ACTIN	5	17	22.7%
CD34	1	4	20%
S100	3	25	10.7%
DESMIN	0	17	0%

GRADE(G1 vs G2 vsG3)	0.13	0.71	8.74	**0.003**	9.90	**0.002**
METASTATIC AT PRESENTATION vs NON METASTATIC	33.54	**0.00**	35.21	**0.00**	35.21	**0.00**
NACT vs UPFRONT SURGERY	1.48	0.22	3.09	0.07	1.82	0.17
ADJUVANT vs NO ADJUVANT	3.23	0.07	4.45	**0.03**	3.62	**0.05**

Table 4: Impact of different variables on 1,3- and 5-year disease free survival on univariate analysis

VARIABLES	IMPACT ON 1 YR DFS		IMPACT ON 3 YR DFS		IMPACT ON 5 YR DFS	
	Chi square	P value	Chi square	P value	Chi square	P value
AGE(≤25 year vs >25 year)	1.42	0.23	6.2	**0.01**	4.0	**0.04**
GENDER(Male vs Female)	0.15	0.69	1.4	0.23	0.73	0.39
TUMOR SIZE ON MRI(≤10 cm vs >10 cm)	0.01	0.89	0.001	0.97	0.04	0.82
STAGE	36.82	**0.00**	40.55	**0.00**	39.77	**0.00**
GRADE(G1 VS G2G3)	2.8	0.09	11.6	**0.001**	7.02	**0.008**
NACT vs UPFRONT SURGERY	0.34	0.56	0.78	0.37	1.52	0.21
ADJUVANT vs NO ADJUVANT	4.2	**0.03**	4.8	**0.02**	3.54	**0.04**