RESEARCH ARTICLE

# Salvage Treatment Experience in Advanced Synovial Sarcoma: a Multicenter Retrospective Analysis of the Anatolian Society of Medical Oncology

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## Abstract

**Background: We aimed to evaluate prognostic factors and response rates to various treatment approaches to patients with synovial sarcoma in an advanced setting. Materials and Methods: We retrospectively reviewed the medical records of 55 patients (18 pts; 32.7% women) diagnosed with synovial sarcomas. Twenty had metastatic disease at the time of diagnosis while the remainder of the study group consisted of patients who developed metastatic or inoperable locally advanced disease during follow up. Results: The median follow up time was 15 months (range: 1-53). Regarding outcomes for the 55 patients, 3 and 5 year overall survival rates were 26% and 14%, respectively. In univariate analyses among demographic factors female gender was associated with a better outcome (p=0.030). Patients with early progressing disease (<2 years) had a worse prognosis when compared to patient group with late relapse, but this difference did not reach statistical significance (p=0.056). According to multivariate Cox regression analysis patients who had undergone metastasectomy had a significant survival advantage (p=0.044). The overall response rate to different salvage chemotherapy regimens given as second line treatment was around 42.9-53.9% for all regimes. There were no statistically significant differences between chemotherapy regimens given in either second or third line settings in terms of overall survival. Conclusions: We observed no major differences in terms of response rate and survival between different salvage chemotherapy regimens. Although metastatic disease still carries a poor prognosis, metastasectomy was found to be associated with improved survival**

**Keywords:** Synovial sarcoma - advanced disease - salvage chemotherapy - prognostic factors - metastasectomy

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## Introduction

The patients with synovial sarcoma have a high recurrence rate and approximately 50% of these patients progress to metastatic stage in the course of the disease (Toyama et al., 2013). Although these tumors usually metastasize to many other organs including lymph nodes, the lungs are the most commonly involved sites of metastasis (Potter et al., 1985).

Metastatic disease of synovial sarcoma has a relatively high response rate (Spurrell et al., 2005; Karavasilis et al., 2008) when compared to other types of soft tissue sarcomas. In the treatment of advanced stage synovial sarcoma, doxorubicin with or without ifosfamide is used as first line chemotherapy. Other chemotherapeutic regimens have failed to show higher success rates therefore doxorubicin based regimens remain the standard of care in the first line setting (Bramwell et al., 2003).

Prognostic factors still have not been fully identified in patients with advanced disease. This is partly because of the rarity of the disease and difficulty in gathering enough number of patients eligible for assessment. We aimed to evaluate clinical and pathological factors associated with disease prognosis and treatment outcome. We also assessed the efficacy of various chemotherapy regimens and surgery in the setting of progression beyond first line chemotherapy.

## Materials and Methods

Between July 2003 and April 2012, a total of 96 patients with the diagnosis of synovial sarcoma from ten cancer

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centers were retrospectively evaluated. The diagnosis of synovial sarcoma was made by histological examination based on the WHO and 1995 Enzinger and Weiss classification also immunohistochemistry stain had been used by local pathology centers. Advanced disease was defined as metastatic disease, local recurrence (LR) not amenable to complete surgical excision or primary tumor not amenable to complete surgical excision. We identified 55 patients having sufficient data in their medical records, with advanced disease eligible for inclusion in the study. Baseline assessment variables including demographic data such as age and gender, history and physical examination, serum chemistry, histopathological results, treatment types and survival data were collected and then entered into a comprehensive data base. Additional treatments received at the time of disease recurrence or relapse and treatment outcomes were also evaluated.

Survival analysis was performed from the time of identification distant metastatic or locally advanced disease. Variables assumed to effect outcome such as age, gender, pathologic subtype, tumor size, localization, type of therapy received in the adjuvant setting, type of surgery for the primary lesion, metastatic surgery, type of salvage chemotherapy were included in the analysis. Response evaluation to chemotherapy were performed by recording the retrospective data of imaging records done every 3 cycles of chemotherapy according to Response Evaluation Criteria In Solid Tumors (RECIST).

*Statistical analysis*

Overall survival (OS) time was calculated from the time of diagnosis of advanced disease to death or last follow-up visit. The probability of OS was estimated by using the Kaplan-Meier method (Kaplan and Meier, 1958). Analysis of the potential prognostic factors was undertaken using Cox's regression. All statistical analyses were performed using SPSS 17.0 statistical software (SPSS, Chicago, IL, USA).

## Results

Study group consisted of 55 patients (18; 32.7% women) with a median age of 38 (range 15-68). The median follow up time was 15 months (range: 1-53). The clinical characteristics of the patients were summarized in Table 1. Most of the primary tumors were located in the lower limbs. The percentage of patients whose tumor size <5 cm was 69.1%. Management of the primary tumors was in accordance with standard care, most patients having undergone surgery as well as radiotherapy. Twenty patients had metastatic disease at the time of diagnosis while the rest of the study group consisted of patients who developed metastatic or inoperable locally advanced disease (n=5) during follow up. Forty-three (78.8%) patients received ifosfamide and doxorubicin combination therapy over the course of the disease. Lung metastasis was the most common metastatic localization where in 36 (65.45%) patients it was the only organ affected by metastatic disease. All deaths were related to progression of synovial sarcoma.

The survival outcomes for the 55 patients, with a median follow up period of 15 months, were as follows: 22 (40%) patients were alive and 33 (60%) patients were dead, additionally 6 (11%) patients remained disease free. The three and five year overall survival rates were%26 and%14, respectively (Figure 1). The median time to onset of advanced disease was 14 months.

**Table 1. Patient Characteristics**

| Characteristic | | Number |
|---|---|---|
| Total number of patients | | 55 |
| Gender | Male | 37 |
| | Female | 18 |
| Age | <35 | 26 |
| | >35 | 29 |
| Histology | Monophasic | 26 |
| | Biphasic | 16 |
| | Poorly differentiated | 7 |
| | Unknown | 6 |
| Tumor grade | 1 | 5 |
| | 2 | 16 |
| | 3 | 28 |
| | Unknown | 6 |
| Site of primary tumor | Extremity | 33 |
| | Truncal | 21 |
| | Head | 1 |
| Stage | 1a/1b | 3/1 |
| | 2a/2b | 10/7 |
| | 3 | 14 |
| | 4 | 20 |
| Tumor size (cm) | <5 | 13 |
| | >5 | 38 |
| | Unknown | 4 |
| Surgery to Primary | Yes | 45 |
| | No | 10 |
| Radiotherapy at diagnosis | Yes | 22 |
| | No | 33 |
| Previous chemotherapy use | Adjustment | 25 |
| | No | 29 |
| Local recurrence | Yes | 5 |
| | No | 50 |
| Development of metastases | Yes | 45 |
| | No | 5 |
| | Unknown | 5 |
| Pattern of metastases | Lung | 36 |
| | Bone | 3 |
| | Node | 3 |
| | Abdomen | 1 |
| | Lung+node | 1 |
| | Lung+bone | 1 |
| Metastasectomies | Yes | 15 |
| | No | 40 |
| Palliative radiotherapy | Yes | 3 |
| | No | 52 |

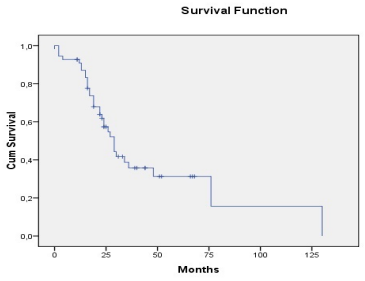


**Figure 1. Kaplan Meier Survival Curve Showing Overall Survival of Advanced Stage Synovial Sarcoma Patients**

*Response rates*

The overall response rate of the 24 chemo-naive patients with advanced disease was 66.6%.The overall

response rate to different salvage chemotherapy regimens given as second line treatment was 53.9% for 13 patients receiving docetaxel-gemcitabine combination chemotherapy regimen, 50% for 10 patients receiving cyclophosphamide/doxorubicin/dacarbazine (CyADIC), 42.9% for 10 patients receiving ifosfamide/mesna/etoposide (IMET) (p>0.05). There were no statistically significant differences between various chemotherapy regimens given in second line in terms of overall survival (Figure 2).

Twenty one patients received third line chemotherapy. Nine patients who received taxane-gemcitabine combination had a response rate of 44.4% while 4 patients receiving IMET had a response rate of 50%. The remaining 8 patients who received various other therapies such as single agent taxane, oral etoposide, cyclophosphamide and vincristine combination had a median response rate of 37%.

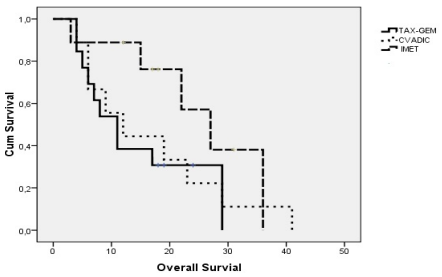


**Figure 2. Kaplan Meier Estimates of Overall Survival in Patients Receiving Different Chemotherapy Regimens**

**Table 2. Univariate Analysis of OS**

| Variable | | OS (%) 3y | p value |
|---|---|---|---|
| Gender | Women | 42* | 0.030 |
| | Men | 16* | |
| Age | <35 | 25 | 0.724 |
| | >35 | 26 | |
| Tumor size (cm) | <5 | 23 | 0.941 |
| | >5 | 29 | |
| Histology | Monophasic | 21 | 0.559 |
| | Biphasic | 25 | |
| | Poorly | | |
| Presentation of advanced disease | Initial | 18 | 0.606 |
| | Late | 34 | |
| Sites | Extremity | 35 | 0.492 |
| | Trunk | 18 | |
| Previous chemotherapy | Yes | 27 | 0.126 |
| | No | 29 | |
| Time to progression (years) | <2 | 19* | 0.056 |
| | >2 | 77* | |
| Metastasectomies | Yes | 59 | 0.008 |
| | No | 13 | |
| Recurrence site | Local | 20 | 0.440 |
| | Distant | 28 | |

*statistically significant

**Table 3. Response Rates to the Most Commonly Used Chemotherapy Regimens**

| Agents | Patient number | Response Rate (%) |
|---|---|---|
| Ifosfamide/Etoposide | 10 | 42 |
| Cyclophosphamide/Doxorubisin/Dacarbazine | 10 | 50 |
| Docetaksel/Gemcitabine | 13 | 53.9 |

*Prognostic factors*:

In univariate analyses among demographic factors female gender was associated with a better outcome (p=0.030). Patients with an early progressing disease (<2 years) had a worse prognosis when compared to patient group with late relapse and however, this difference did not reach statistical significance (p=0.056). There was no correlation between other demographic and histopathologic factors and survival.

According to multivariate cox regression analysis patients who had undergone metastasectomy had a significant survival advantage [p=0.044, B: 0.217 (95% CI: 0.049-0.957)] (Table 2).

## Discussion

The available agents for the first line treatment of advanced stage soft tissue sarcomas remain limited. Synovial sarcoma is a rare subtypes of soft tissue sarcoma (STS) and have a relatively high preponderance to distant metastasis. It has a higher response rate to chemotherapy when compared to other subtypes (Van Glabbeke et al., 1999; Spurrell et al., 2005; Sleijfer et al., 2010). More than half of the patients in our cohort had an objective response to palliative chemotherapy. The higher response rate achieved with chemotherapy might contribute to the more favorable outcome and the better survival of patients with these tumors. Karavasilis et al (Karavasilis et al., 2008) in a series of 488 advanced STS including SS, conclude that palliative chemotherapy should be regarded as a standard treatment option, with approximately half of patients deriving clinical benefit. Based on this characteristic combined multiagent chemotherapy has been advised for treatment in this setting. However the optimal treatment strategy is still unclarified due to scarcity of data of this rare disease (Spurrell et al., 2005; Ferrari et al., 2012).

Our primary aim in this study was to outline possible prognostic factors affecting disease outcome and analyze the efficacy of various salvage treatment options in a data set of patients from multicenter cohort.

The study groups 5 year survival rate was worse when compared to literature (Spurrell et al., 2005; Ferrari et al., 2012). Five year overall survival was reported around 30% in the published studies. The reason for this observation could be that the both the chemo naive population and the number of patients receiving metastatic surgery was high in other studies (Spurrell et al., 2005; Ferrari et al., 2012). In contrast Palmerini et al. (2009) reported 5 year survival rate as 10% for metastatic disease which was very similar to our observations.

The female gender was observed to have a higher survival rate and this was found to be statistically significant in univariate analysis. In the literature male sex is associated with decreased survival (Trassard et al., 2001). SYT-SSX1 fusion transcript has a higher prevalence in males and it has been shown that patients carrying this fusion type have an increased risk of early distant recurrence (Canter et al., 2008). One other explanation could be the slower clearance rate of chemotherapeutic agents in women (Sleijfer et al., 2010).

Metastasectomy was found to be a favorable factor

in multivariate analysis. Patients who had a resection of their metastatic lesions had a higher survival (p=0.008). However this finding is not confirmed in a study with a larger series of patients (Spurrell et al., 2005). Ferrari et al. (2012) has also reported that metastasectomy and second remission is associated with better survival in the setting of advanced synovial sarcoma. We also observed that metastasectomy was more beneficial in the patient group who developed metastasis later in the course of the disease (p=0.023).

Whether early relapse is an adverse prognostic factor is controversial. While early relapse (<18 months) has been reported to be significantly associated with worse prognosis (van Geel et al., 1996; Palmerini et al., 2009) only reported a trend for shorter survival. In our study, we observed a strong trend for shorter overall survival in patients whose disease progressed before two years (p=0.056).

The response rates of chemo-naive patients presenting with advanced disease to standard ifosfamide doxorubicin treatment were in accordance with the literature. In our retrospective analysis we also aimed to assess the difference between various salvage chemotherapy protocols especially in terms of response rate. In the literature much of the existing data is derived from the analysis of subgroups of synovial sarcoma patients consisting of a relatively small number of patients In recent years, docetaxel and gemcitabine combination gained attention as a salvage regimen in advanced and metastatic soft tissue sarcoma patients (Kaya et al., 2012). In the mentioned study which included various other histologic subtypes of soft tissue sarcomas in its study group which have usually lower response to chemotherapies; the response rate for docetaxel plus gemcitabine combination was reported as low as 20.9%. On the other hand two phase 2 trials with more homogenous study populations reported response rates around 55% which is very similar to our finding (Hensley et al., 2002; Lee et al., 2012). We did not detect any differences both in terms of response and survival rates when docetaxel gemcitabine combination chemotherapy was compared with either CyADIC or IMET treatments. Other salvage regimens in the setting of metastatic soft tissue sarcoma were also reported to have similar response rates (Elias, 1994). We are aware of that our results are subject to the caveats of retrospective analysis of a multicenter study with a relatively small number of patients.

In conclusion, salvage chemotherapy regimens do not carry on major differences in terms of survival and response rate. Metastasectomy is still the main cornerstone of treatment and eligible patients should be offered this choice in centers with experience in this field. The outcome of patients progressing after first line chemotherapy remains dismal and further research is needed for more effective treatments affecting a disease with a young population of cancer patients.

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