Archives of Orthopaedic and Trauma Surgery (2019) 139:443–449
https://doi.org/10.1007/s00402-018-3059-x

ORTHOPAEDIC SURGERY

Surgical excision and not chemotherapy is the most powerful modality in treating synovial sarcoma: the UK's North East experience

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Received: 6 July 2018 / Published online: 8 November 2018

Abstract

Background and purpose We reviewed our experience of synovial sarcoma to identify factors predictive of local recurrence and overall survival, the impact of chemotherapy and outcomes after surgical excision alone.

Materials and methods 81 patients were treated between 1997 and 2014 of mean age 39 years (8–78). Tumours were in the extremity in 55 (67%). 9 patients presented with metastases and 10 with unresectable disease. Mean follow-up was 3.7 years (SD 3.8). Treatment groups were palliative, surgery only, surgery and radiotherapy, or surgery with chemotherapy (with or without radiotherapy).

Results Local recurrence-free survival (LRFS) was 73% at 5 years, and 68% at 10 and 15 years. In multivariate analysis, positive surgical margins were an independent predictor of LRFS. Overall survival (OS) was 50% at 5 years for all patients, and 62% at 5 years for those treated with curative intent. Larger tumour size and non-extremity locations were predictors of poorer OS. Patients who had chemotherapy did not have significantly better OS or LRS than others.

Interpretation These results show that where feasible, curative resection should not be delayed for chemotherapy. Treatment with surgery only can be associated with good outcomes in selected patients with smaller extremity tumours; although our series is small.

Keywords Synovial sarcoma · Chemotherapy · Radiotherapy

Introduction

Synovial sarcomas form a group of malignant tumours arising in the connective tissues and are characterized by a specific chromosomal translocation t(X;18)(p11;q11) leading to formation of a SS18-SSX fusion gene. Although mesenchymal in origin these tumours display a variable degree of epithelial differentiation, including gland formation. Synovial sarcoma is further classified morphologically as biphasic, monophasic or poorly differentiated [1–3]. Synovial sarcoma may occur at any age, but more than half of patients are teenagers and young adults [1]. Most tumours arise in the deep soft tissues of the extremities, often in a juxta articular location. However, tumours also occur in other locations such as the head and neck [4]. Synovial sarcoma demonstrates a spectrum of behaviour, with some tumours pursuing an indolent course with a long pre-diagnostic history. Many tumours are painless which can contribute to diagnostic delay [5, 6].

Wherever feasible, surgery is the mainstay of treatment. Adjuvant radiotherapy is used for loco-regional control of larger tumours or those that cannot be excised with a wide margin [7]. The use of chemotherapy is more controversial, with some studies suggesting a benefit [8–11], but others not [12–15]. Some data suggest that a subgroup of synovial sarcomas (small distal extremity tumours) can be successfully treated with surgery alone [16].

We were therefore interested in reviewing our experience of synovial sarcoma in order to determine which factors influence outcomes in our service and whether our approach has been appropriate.

We specifically aimed to:

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- Identify factors influencing local recurrence and overall survival.
- Investigate the impact of chemotherapy.
- Assess the outcome of patients treated with surgery alone.

Methods

This was a retrospective study of patients treated within the North of England Bone and Soft Tissue Tumour Service between 1997 and 2014. Patients were identified from a prospectively collected computerized database and details checked against clinical records.

Our practice has been to offer postoperative radiotherapy where feasible for better loco-regional control to all patients except those who have small superficial tumours with widely excised margins. We consider neoadjuvant or adjuvant chemotherapy for patients who have tumours larger than 5 cm, or which are deep or centrally located.

For the analysis, patients were classified into four treatment groups. These were: treatment with palliative intent, surgery only, surgery and radiotherapy alone, surgery and chemotherapy (with or without radiotherapy).

Statistical analysis

Kaplan–Meier survival analyses for overall survival and local recurrence-free survival were conducted. Univariate analysis was used to determine significant prognostic factors (log-rank test). Factors reaching significance were then used in a multivariate Cox model to identify independent predictors of outcome. Finally, overall and local recurrence-free survivals were estimated for each of the treatment groups after adjusting for the independent prognostic factors in the second step of the Cox multivariate survival analysis. We used SPSS version 21 for all analysis.

The variables used in the model were age (≤ 25 or > 25 years), tumour size (single maximum dimension from CT or MRI), anatomical location (extremity vs. non-extremity), and surgical margin status [positive (intra-lesional), or negative (marginal or wide)].

Results

81 patients were identified. There were 40 (52%) females and 41 (48%) males. Mean age at presentation was 39 years (range 8–78 years). Mean maximum tumour diameter was 8.3 cm (SD 4.3, range 1–26 cm, $n = 71$). The tumour size could not be collected in ten cases.

Most tumours (55/81, 67%) were located in the extremities. Of the remainder, 10 were located in the thorax, 5 in the head and neck, 5 in the abdomen/pelvis, 5 in the retroperitoneum and 1 in the spine. Maximum tumour diameter varied by anatomical location, being an average of 7.2 cm in the extremity, 6.2 cm in the head and neck and 12.5 cm in thoracic or abdominal locations. Extremity and head and neck tumours were significantly smaller than non-extremity tumours ($p < 0.001$ and $p = 0.04$, respectively, one-way ANOVA with Bonferroni correction).

Nineteen patients were treated with palliative intent: 9 (11%) patients with metastasis at presentation and 10 (12%) whose tumours were inoperable because of local extension or fitness for surgery. Palliative treatment included de-bulking surgery, chemotherapy or radiotherapy and general supportive care (Fig. 1).

The remaining 62 patients received treatment with curative intent including surgery. These patients fell into three groups: surgery only, surgery and radiotherapy, or surgery with chemotherapy (with or without radiotherapy) (Table 1).

Patients in the first group were treated with surgical excision only ($n = 13$). Tumours were located in foot/ankle in 5 cases, the thigh in 3, around the knee in 2 and one each around elbow, cardiac atrium and gastric antrum. 4 patients had primary amputation, 8 patients had wide surgical excision, and one patient (cardiac atrium) had marginal excision and mitral value reconstruction. The average size of tumour in this group was smaller than the other groups (Table 1). Mean follow-up was 5.7 years (0.4–11 years). Two patients died of metastatic disease.

Patients in the second group had surgery and adjuvant radiotherapy but no chemotherapy ($n = 11$). The mean follow-up of this group was 5.8 years (range 1.1–15.8 years). Two of these patients died. Tumour sizes of these patients were not known.

Patients who had chemotherapy were placed into the final group ($n = 38$); 18 had surgery, chemotherapy and postoperative radiotherapy, and 20 had surgery and chemotherapy alone. The mean follow-up of this group was 3.8 years (0.3–14.6 years).

Chemotherapy regimes mostly comprised six cycles of ifosfamide or doxorubicin. This was given as neoadjuvant in 21, adjuvant in 20, and both in 6 cases. The average survival of patients who had neoadjuvant chemotherapy was 3.7 years. Of these patients, 10 were alive without any evidence of disease, 3 patients were alive with disease and 8 patients had died.

Histological response to neoadjuvant chemotherapy was assessed in 21 resection specimens. The necrosis rate was reported in 12: this was from 10 to 25% in 7 patients, 30 and 40% in 2 and 90% in 2 patients. The remaining 9 patients in whom the exact necrosis rate was not reported had overall poor response to chemotherapy with large areas of high cellularity and high rates of mitosis.

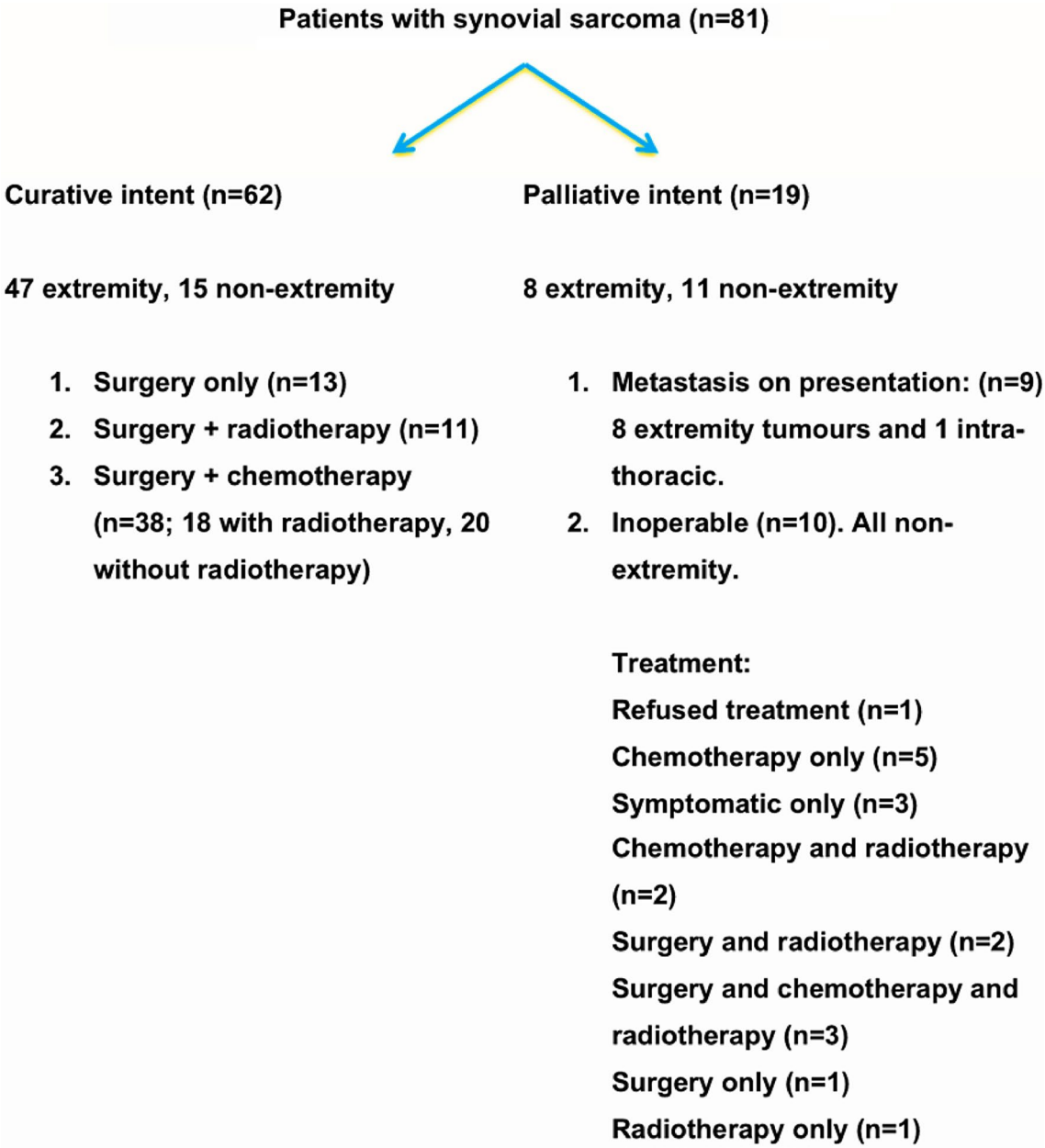

Fig. 1 Treatment groups

Table 1 Patient and tumour characteristics by treatment group

Treatment modality	*N*	Mean age (SD)	Mean maximum diameter (SD)	Positive margins	Location		Local recurrences (%)	Mean Kaplan–Meier survival in years (SE)
					Extremity (%)	Non-extremity		
Palliative intent	19	38 (15.2)	12 (4.5)	2 (10.5%)	8 (42)	11 (58%)	2 (15%)	1.01 (0.2)
Surgery only	13	28.1 (9.7)	3.2 (4)	0	11 (85)	2 (15%)	1 (7%)	9.3 (1)
Surgery and radiotherapy	11	35.3 (12.4)	4.9 (4.2)	0	11 (100)	0	0	11.9 (2.2)
Surgery and chemotherapy	38	31.6 (12.2)	9.4 (5.3)	10 (26.3%)	25 (66)	13 (34%)	11 (78%)	7.9 (1.1)
Total	81	39 (12.9)	8.3 (5.4)	12 (14.8%)	55 (68)	26 (32%)	–	8.3 (0.8)

Local recurrence-free survival

There were local recurrences in 14 patients (17.3%). The local recurrence-free survival was 73% at 5 years, and 68% at 10 and 15 years (SD 0.07). The majority of local recurrences (78%) occurred in the group of patients treated with surgery and chemotherapy (Table 1).

Of these 14 patients, two are alive while the remaining 12 died of metastatic disease. The two survivors were both in the group treated with surgery and chemotherapy. The 12 patients who died had local recurrences in lower extremity (7 patients), head and neck (2 patients) and thorax/abdomen (5 patients); and died of metastatic disease at an average follow-up of 2.7 years. Overall the rate of local recurrence in the lower extremity was 16%, head and neck 40%, and thorax/abdomen 31%.

In univariate analysis, significant prognostic factors were tumour location and surgical margin status. Age was not a significant prognostic factor; tumour size approached but was not significant (Table 2). Location, status of the surgical margins and tumour size (because it approached significance) were used in Cox multivariate analysis (Table 3). In this analysis, the only significant factor for local recurrence was surgical margin status ($p=0.003$); tumour size and location were not significant. In the second step of Cox analysis, the LRFS in the different treatment groups was estimated at the mean of significantly important factors. There was no difference in the LRFS in patients who received chemotherapy in addition to surgical excision compared to those in other groups (Table 3).

Overall survival

At last follow-up, 34 patients (42%) had died of sarcoma. Of the remaining 48 (58%) patients, 13 were alive with metastasis and 35 were alive with no evidence of active disease. The Kaplan–Meier (Fig. 2) 5-year disease specific survival was 50% (SE 0.06); and at 10 and 15.8 years was 44% (SE 0.06).

Overall survival of patients treated with curative intent was 62% (SE 0.07) at 5 years and 60% (SE 0.07) at 15.8 years. The overall survival of patients treated with palliative intent was 14% (SE 0.09) at 2 years, a statistically significant difference ($p \leq 0.001$, log-rank test).

Univariate analysis showed that positive surgical margins, non-extremity location and size greater than 5 cm were significant adverse prognostic factors (Table 2). In Cox multivariate analysis, tumour size and location remained significant independent prognostic factors for overall survival; surgical margin status was not (Table 3).

Finally, Cox regression analysis showed that at the mean of significantly important prognostic factors, there was no statistically significant difference in overall survival of patients who received chemotherapy and surgical excision compared to those who received radiotherapy and surgical

Table 2 Univariate analysis for significance of prognostic factors associated with overall survival and local recurrence-free survival

Variable	LRFS mean (years)		*p* value	Overall survival mean (years)		*p* value
Age	< 25	12.9	0.2	< 25	8.5	0.5
	> 25	10.9		> 25	8	
Tumour size	< 5 cm	10.1	0.05	< 5 cm	14.4	< 0.001
	> 5 cm	14.3		> 5 cm	6.9	
Location	Extremity	13	< 0.001	Extremity	9.7	< 0.001
	Non-extremity	4.4		Non-extremity	2.9	
Surgical margins	Positive	2.8	< 0.001	Positive	3	0.03
	Negative	13.8		Negative	9	

Table 3 Hazard ratios for significant prognostic factors associated with overall survival and local recurrence-free survival; and each of the treatment modality, after adjustment for prognostic factors

Variable	Hazard ratio LRFS	*p* value	Hazard ratio Overall survival	*p* value
Extremity location	0.72	0.3	0.65	0.04
Tumour size	1.1	0.1	1.107	0.02
Surgical margins	0.11	0.003	0.68	0.4
Treatment				
Surgery + chemotherapy	Reference	Reference	Reference	Reference
Surgery + radiotherapy	0.00	0.97	0.00	0.97
Surgery only	0.00	0.97	0.35	0.33
Palliative	1.48	0.67	8.7	< 0.001

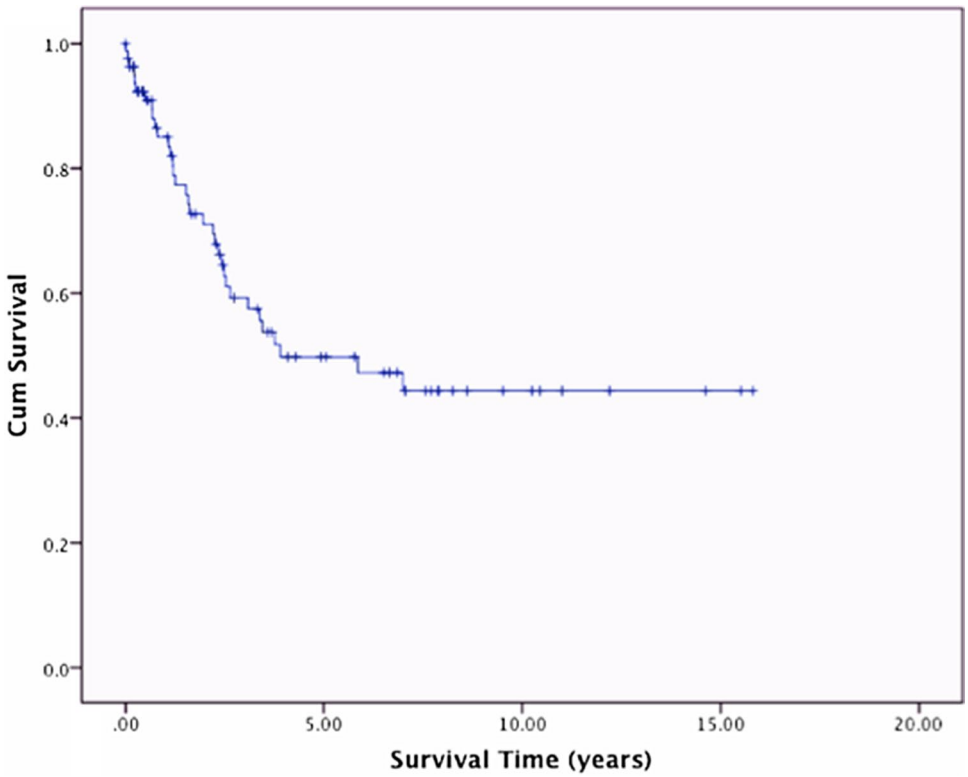

Fig. 2 Kaplan–Meier curve for overall survival

excision, or surgery only; while patients treated with palliative intent had significantly reduced survival (Table 3; Fig. 3).

Discussion

This retrospective observational series has reviewed the experience of management and outcomes of patients with synovial sarcoma in a single centre. Our aim was to identify independent prognostic factors affecting local recurrence and overall survival, investigate if the addition of chemotherapy was associated with improved outcomes and assess the outcomes of patients treated with surgery alone.

Chemotherapy group was the most diverse of all the four groups of patients. Patients in this group had larger tumours (mean 9.3 cm), and about one-third of these tumours were in the non-extremity locations (thorax, abdomen, pelvis and head/neck). Both these variables have been shown to be independent factors of poorer prognosis in other studies [7]. In recognition of this, these are patients for whom we are more likely to recommend chemotherapy. However, in our analysis we found the addition of chemotherapy did not have a significant effect on overall survival or local recurrence. We recognize that these were not directly comparable groups and the best method would be to conduct a randomized control trial comparing the effect of chemotherapy in the same group of patients. However due to ethical reasons such a trial is difficult to arrange and multivariate Cox survival analysis is a widely used tool that is used frequently in such situations.

Our multivariate analysis showed that status of the excised margins was the only significant independent prognostic factor for local recurrence; and larger tumour size and non-extremity location were significant independent prognostic factors for poor overall survival. Similar findings have been reported in other studies [17, 18]. We found that most larger tumours were in the non-extremity locations, and this may explain, at least partly, the effect of location on OS; besides the difficulties in obtaining curative resection due to anatomical challenges. We did not find age as a significantly important factor for OS or LRS, although increasing age has been shown to be associated with poor prognosis and high risk of recurrence in other studies [17, 19]. We used age as a dichotomous variable [20] in this study; we also modelled it as a continuous variable and its effects remained insignificant (data not presented).

Overall survival of patients treated with curative intent (60% at 15 years) is the same as that of reported in other similar large studies (64–70%) [9, 14]. In our study, most of the deaths (60%) have been in the first 2 years, and the last death was at 7 years. We did not notice late treatment failures as reported in another study, for up to 15 years [14], however we are keeping the patients in regular follow-up.

One of the aims of our study was to assess the outcome of patients who were treated with surgery alone. The results

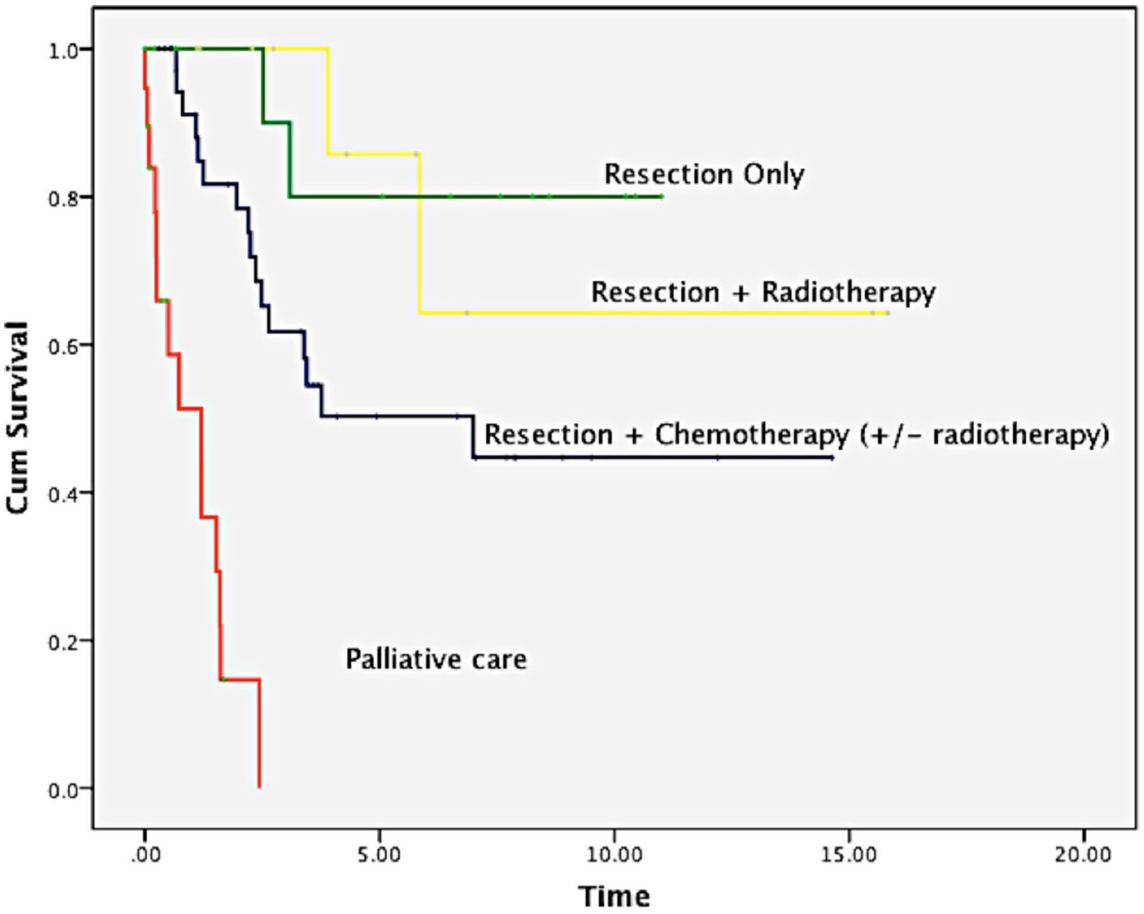

Fig. 3 Kaplan–Meier survival curve by individual treatment groups

of this study showed that in a select group of patients, surgical excision alone can lead to long-term local and systemic control; providing equivalent long-term results similar to that of the addition of chemotherapy and radiotherapy. The characteristic feature of this group is smaller sized tumours, which are located in the extremity and were amenable to wide resection. However, due to a smaller number of patients in this group, we cannot suggest considering surgical excision as the only treatment modality for the treatment of smaller size peripheral and superficial tumours; and therefore addition of radiotherapy for better loco-regional control in this group remains the gold standard. However, given the poor overall response rates of tumours to the chemotherapy (clinically and histologically to neoadjuvant chemotherapy), suggesting that it does not have any substantial additional effect of improving survival, we suggest that surgical excision of synovial sarcomas should not be delayed for neoadjuvant treatments, where possible because surgical excision is the most powerful treatment modality.

Radiotherapy was used as an adjuvant treatment in this series for loco-regional control. Our results show that LRS and OS of patients who only had adjuvant radiotherapy was not significantly different from patients who had adjuvant chemotherapy alone or in addition to the radiotherapy (chemotherapy + surgery group). In this series, adjuvant radiotherapy was used for a select group of patients with small extremity tumours, with good outcome; this indicates towards the fact that synovial sarcoma is a localized disease in the earlier stages. Ferrari et al. [9] reported 5 years LRS of 57% for patients who had marginal excisions of the tumour and adjuvant radiotherapy, while LRS dropped to only 7% in such patients who did not had adjuvant radiotherapy. Therefore, although we cannot infer meaningful results regarding the efficacy of radiotherapy from our study, we favor using adjuvant radiotherapy for better loco-regional control [21].

Strengths and weakness

The main strengths of our single-centre study are the large number of patients and length of follow-up. The practice at our institution is such that we did not have patients with larger size tumours who were treated without adjuvant treatment. We however used the Cox multivariate survival

analysis to account for the effects of independent prognostic factors on LRS (surgical margins) and OS (tumour size and location), and then assess for the effects of chemotherapy. Despite removal of the effects of tumour size, location and surgical margins, chemotherapy did not have any beneficial effects on the LRS and OS. We are aware that a prospective randomized trial would be a more powerful study design but due to ethical and practicability reasons it is difficult to arrange. Our data regarding assessment of histological response to chemotherapy was less objective and therefore we did not include it into the analysis. Besides it is reported that in soft tissue tumours, histological characteristics like mitotic activity and necrosis on core biopsy are such parameters that are not representative of the entire tumour and the not reproducible among different pathologists [22].

Summary

In summary, our results show that surgical excision is the mainstay of treatment for synovial sarcoma. Patients with small extremity tumours can be treated with surgery alone, but this has to be further supported by a larger series of patients in future to include children and adults. We strongly suggest that wherever curative treatment is possible, surgical resection shall not be delayed for neoadjuvant chemotherapy.

Compliance with ethical standards

Conflict of interest We hereby state that "no" financial or personal gains of any kind have been received by any of the authors in preparation of this manuscript. Dr. Munir Khan stating on behalf of all the authors of this manuscript.

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