European Journal of Surgical Oncology 45 (2019) 254–260

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Synovial sarcoma: Do children do better?

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ARTICLE INFO

Article history:
Accepted 3 July 2018
Available online 20 July 2018

Keywords:
Synovial sarcoma
Soft tissue sarcoma
Prognsotic factors
Cancer-specific survival

ABSTRACT

Objectives: Synovial sarcoma, a distinct subtype of soft tissue sarcomas (STS), is typically found in young patients. Long history of symptoms and heterogeneous clinical presentation sometimes delays diagnosis. Children have been reported to have a better prognosis than adults in some series.
The main emphasis of this study was to determine differences between children and adults and to investigate prognostic factors regarding cancer specific survival (CSS).
Methods: 248 patients treated between 1982 and 2014 at one department were included. Mean age was 37.0 years, including 43 patients <16 years. Demographic, pathology- and treatment-related information was ascertained. Median follow-up was 5.2 years.
Results: Median duration of symptoms was 11.5 months in children and 12 months in adults ($p = 0.238$). Patients with a prior unplanned excision had a significantly longer duration of symptoms ($p = 0.001$). No difference was present between children and adults regarding tumour size, site, grade and superficial/deep location. Treatment was with surgical excision and (usually) adjuvant radiotherapy but five patients received preoperative radiotherapy and 43 patients chemotherapy. In patients treated with curative intent, five-year CSS rates were 75.5% for adults and 89.0% for children, with 10-year CSS rates of 56.1% and 82.2% ($p = 0.026$).
In multivariate analysis, large tumour size ($p < 0.005$) and patient age ($p = 0.024$) were associated with worse CSS, irrespective of tumour location and site.
Conclusion: Clinical presentation of synovial sarcoma is similar in children and adults, with no significant difference in tumour size, site, grade or location. Small tumour size and young patient age are independent positive prognostic factors influencing CSS.

Introduction

With an incidence of 1.3 per 1 million population, synovial sarcomas account for about 6% of all soft tissue sarcomas (STS) [1,2]. Patients seem to benefit more from chemotherapy (CTX) than patients with other subtypes of STS and tend to develop local recurrence (LR) and metastasis at a later stage [3,4]. Patients with synovial sarcoma tend to be younger, compared to patients with other STS subtypes, with a mean age of 35 [5].

The translocation t (X;18) (p11;q11) is specific for synovial sarcoma and facilitates differentiation from other types of STS [6]. The monophasic subtype, consisting of spindle cells only, accounts for 50–60% of all synovial sarcomas. Less common is the biphasic subtype in 20–30%, composed of spindle cells and plump epithelial cells, and a poorly differentiated subtype in the remaining 10–20% [7]. The term “synovial sarcoma” is misleading, as this tumour neither originates from the synovium nor develops within a joint. Though synovial sarcomas predominantly arise in the lower and upper limbs, cases in the head/neck, retroperitoneal and abdominal region have been described as well [8,9].

The main surgical principle is en bloc resection of the tumour and the biopsy tract. Adjuvant radiotherapy may be considered for patients with tumours exceeding 5 cm in size [10]. Chemotherapy with ifosfamide and doxorubicin should be considered for patients with advanced disease, often leading to satisfactory response-rates [11]. There is less certainty about the role of adjuvant chemotherapy.

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https://doi.org/10.1016/j.ejso.2018.07.006
0748-7983/

Clinical features suggestive of a soft tissue sarcoma established by the *National Institute for Health and Care Excellence (NICE)* are often inapplicable to synovial sarcoma patients. In comparison to both bone and other soft tissue sarcomas, the duration of symptoms is rather long and complaints may include palpable masses or enlarging lumps which may be painful [12,13].

Osseous or neurovascular invasion, adult age and large tumour size have been linked with a worse prognosis [14]. As tumour size is reported to increase with age, however, it has to be questioned whether age alone constitutes a reliable prognostic factor [9].

The aim of this study was to analyse the difference in clinical presentation and treatment between children and adults. Moreover, parameters associated with cancer-specific survival (CSS) were investigated.

Patients and methods

Study population

Between September 1982 and August 2014, 339 patients were treated for synovial sarcoma at our unit. Seventy-three patients with a follow-up less than 12 months and those presenting with recurrence were excluded.

From the remaining 248 patients, demographic (age and gender), therapeutic (unplanned excision, adjuvant therapy) and pathological variables (grade, stage, anatomical site, size, depth) were ascertained.

Staging was performed using MRI and/or CT-scans of the tumour and CT-scans of the chest. All patients underwent biopsy and treatment was planned through our dedicated sarcoma multidisciplinary team. Surgical excision was performed in most patients but was sometimes not carried out if there was rapidly progressive disease or if the patient had comorbidities preventing surgery.

Statistical analysis

IBM SPSS Statistics 23 was used for statistical analysis. *Pearson's Chi-Squared-Test* was carried out to determine the relationship between categorial variables. For continuous variables, means with standard deviations (SD) or medians with IQR were used. Means between two groups were compared with T-tests or with Mann-Whitney U-tests. Kruskal-Wallis-tests were used for comparison of means between more than two groups.

The time from date of diagnosis to death or last follow-up visit was used to estimate CSS. Patients with metastasis at time of diagnosis ($n = 25$) were excluded from survival analysis.

The *Kaplan-Meier* method and log-rank test were used to estimate CSS. For these analyses, continuous variables as tumour size and patient age were converted into categorial variables (patient age – children vs. adults; tumour size – cut-offs set at 5 and 10 cm). Univariate and multivariate models to identify impact of demographic, tumour- and treatment-related features were calculated by *Cox* regression. Hazard ratios (HR) and 95% confidence intervals (95%CI) were ascertained. For these analyses, patient age and tumour size were then used as continuous variables, in order to minimise information loss. A two-sided p-value less than 0.05 was accepted as statistically significant. Throughout the time period of this trial chemotherapy was used selectively for some younger people with large, deep tumours in order to try and downstage the tumour prior to surgery. Radiotherapy was used postoperatively in all cases of large or deep tumours undergoing excision and also in superficial tumours, unless wide margins of excision were achieved. Therefore, adjuvant chemotherapy and radiotherapy were not incorporated in the survival analyses.

In the multivariate model, patient age and tumour size (both as a continuous variable) were included alongside with tumour depth and site.

Results

124 patients were male (50.0%) and 124 female (50.0%). The median follow-up time was 5.2 years (interquartile range [IQR]: 2.3–7.9 years). The mean age was 37.0 years (range 2–83 years). 43 patients (17.3%) were 16 years or younger at time of diagnosis and were therefore classified as paediatric cases. The distribution of pretreatment features, pathological and treatment related factors between children and adults is shown in Table 1. Altogether, 124 individuals (50.0%) had undergone some kind of invasive procedure prior to referral, including open biopsy in 27 cases and unplanned excision in 97, with children and adults equally affected (X^2: $p = 0.274$).

61 patients had tumours located in the upper limbs (24.6%), 172 in the lower limbs (69.4%) and 15 individuals had tumours located in the trunk (6.0%). The most common site was the thigh in 58 cases, followed by the foot in 37, forearm in 30, and knee region in 26 cases. Four tumours were purely intra-articular.

The median overall tumour size of the evaluable cases was 6 cm (IQR: 4–9 cm). The exact size could not be estimated in 41 patients due to previous interventions. Tumour size did not differ significantly between adult and paediatric patients (median: 6.0 cm vs. 5.0 cm; U test: $p = 0.059$). In comparison to children, adult patients rather tended to present with metastatic disease at time of diagnosis (X^2: $p = 0.063$).

6 patients were staged as being UICC-stage I (2.4%) at the time of diagnosis, 70 patients UICC-stage IIA (28.2%), 71 patients with UICC-stage IIB (28.6%), 51 with stage III (20.6%) and 25 with stage IV (10.1%) In 29 patients (10.1%), the stage could not be determined due to missing information. UICC-stage did not significantly differ between children and adults (X^2: $p = 0.221$).

The median duration of symptoms in all patients was 12 months (IQR: 4.6–36.0 months). 31 patients (12.5%) reported symptoms existing for more than 5 years prior to diagnosis. Patients with a prior unplanned excision had a significantly longer median history of symptoms as compared with those who had undergone a prior unplanned excision or had been referred directly to our institution (24 months vs. 12 months; U test: $p = 0.001$). Patients with superifically located tumours reported a median history of symptoms lasting 2.0 years, whereas deeply located tumours had just been first noticed 12 months prior to diagnosis (*U* test; $p = 0.010$). The median duration of symptoms in children was 11.5 months as compared to 12.0 months in adults (U test: $p = 0.238$).

No significant differences concerning history of symptoms were found for gender (U test: $p = 0.640$), tumour size (Kruskal-Wallis: $p = 0.100$), tumour stage (Kruskal-Wallis: $p = 0.415$), tumour grade (Kruskal-Wallis: $p = 0.345$), limbs vs. trunk (T-test: $p = 0.116$) and presence of metastasis at time of diagnosis (U test: $p = 0.688$).

Preoperative radiotherapy was used in five patients in order to improve the resectability (2.3%). Chemotherapy was used in 18.6% of children and 19.0% of adults and was mostly neoadjuvant in an attempt to shrink the tumour prior to surgery. Adjuvant radiotherapy was used according to national guidelines and was used in cases where marginal or intralesional margins were achieved and for larger tumours. Surgical margin status could be ascertained in 137 cases. Wide margins were obtained in 49 cases (35.8%), marginal margins in 61 (44.5%) and intralesional margins in 15 (10.9%). Interestingly, wide margins were achieved in the majority of paediatric patients (56.5%), but only in 31.6% of adults (X^2: $p = 0.067$).

Local recurrence occurred in 32 patients (12.9%) after a median of 3.1 years, of whom two patients already had and 16 subsequently

Table 1
Differences in clinical presentation and outcome between paediatric and adult patients.

		Children (n = 43) No. (%)	Adults (n = 205) No. (%)	p-value
Sex	Male	26 (60.5)	98 (47.8)	0.131
	Female	17 (39.5)	107 (52.2)	
Duration of symptoms	< 1 year	22 (66.7)	87 (55.8)	0.250
	> 1 year	11 (33.3)	69 (44.2)	
Unplanned excision	No	23 (53.5)	128 (62.4)	0.274
	Yes	20 (46.5)	77 (37.6)	
Location	Superficial	6 (14.6)	42 (21.9)	0.298
	Deep	35 (85.4)	150 (78.1)	
Side	Left	20 (46.5)	99 (48.8)	0.788
	Right	23 (53.5)	104 (51.2)	
Site	Upper limbs	7 (16.3)	54 (26.5)	0.370
	Lower limbs	33 (76.7)	138 (67.6)	
	Trunk	3 (7.0)	12 (5.9)	
Grade	G1	3 (7.1)	4 (2.1)	0.219
	G2	22 (52.4)	108 (56.5)	
	G3	17 (40.5)	79 (41.4)	
Size	< 5 cm	17 (48.6)	59 (32.8)	0.200
	5 – 10 cm	12 (34.3)	84 (46.1)	
	> 10 cm	6 (17.1)	38 (21.1)	
Stage	I	2 (5.1)	4 (2.2)	0.221
	IIA	16 (41.0)	54 (29.3)	
	IIB	12 (30.8)	59 (32.1)	
	III	8 (20.5)	43 (23.4)	
	IV	1 (2.6)	24 (13.0)	
Primary metastasis	No	42 (97.7)	181 (88.3)	0.063
	Yes	1 (2.3)	24 (11.7)	
Amputation	No	31 (88.6)	143 (79.0)	0.191
	Yes	4 (11.4)	38 (21.0)	
Resection margins	Intralesional	0 (0.0)	15 (13.2)	0.067
	Marginal	9 (39.1)	52 (45.6)	
	Wide	13 (56.5)	36 (31.6)	
	"Radical"	1 (4.3)	11 (9.6)	
Chemotherapy	No	35 (81.4)	166 (81.0)	0.949
	Yes	8 (18.6)	39 (19.0)	
Local recurrence	No	38 (88.4)	178 (86.8)	0.784
	Yes	5 (11.6)	27 (13.2)	
Secondary metastasis	No	34 (79.1)	118 (57.6)	**0.008**
	Yes	9 (20.9)	87 (42.4)	
Death	No	34 (79.1)	110 (53.7)	**0.002**
	Yes	9 (20.9)	95 (46.3)	

Bold figures show those with significance (ie p<0.05).

developed, distant metastasis. Median time interval from local recurrence to distant metastasis was 1.8 years. Local recurrence arose in five of the 49 patients with wide margins (10.2%), in 11 of the 61 patients with marginal margins (18.0%) and in four of the 15 patients with intralesional margins (26.7%); (X^2: p = 0.351).

After a median follow-up of 5.2 years, 118 patients had no evidence of disease (47.6%), 26 patients were alive with disease (10.5%), 80 patients had died of disease (32.3%) and 24 patients died due to other causes (9.7%).

The 5-year CSS rate for patients with metastasis at time of diagnosis (Stage IV) was 22.6%, in comparison with the 5- and 10-year CSS rates of 78.1% and 60.3% for patients with localised disease undergoing surgery (log-rank-test: p < 0.005). Consequently, those 25 patients with metastatic disease at time of diagnosis were excluded from further survival analyses.

With 5- and 10-year CSS rates of 89.0% and 78.2%, children had a significantly better prognosis than adults with CSS rates being 75.5% and 56.1% respectively (log-rank-test: p = 0.026 Fig. 1). Patients with tumours exceeding 10 cm in size had a significantly worse prognosis in comparison to patients with tumours sized between 5 and 10 cm or synovial sarcomas smaller than 5 cm (log-rank-test; p < 0.005, Fig. 2).

Five- and 10-year risks of LR were estimated at 14.5% and 16.8% for adult patients and 13.6% at both time points for paediatric patients (p = 0.405). Corresponding 5- and 10-year risks for distant

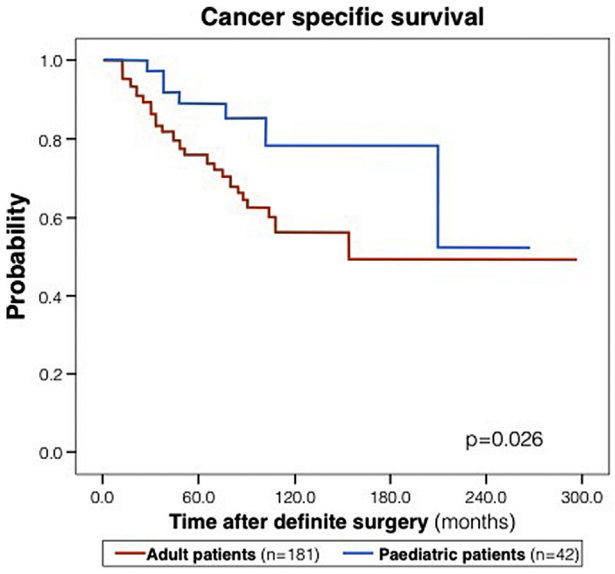

Fig. 1. Differences in CSS between paediatric and adult patients.

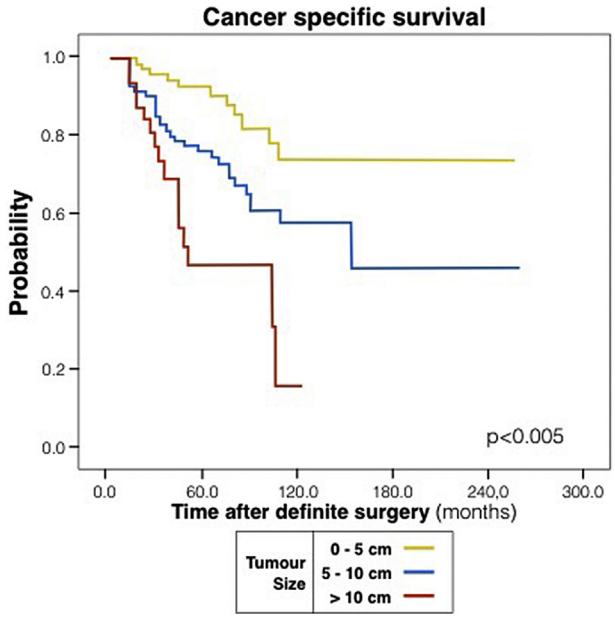

Fig. 2. Kaplan-Meier survival curve showing disparities in CSS depending on tumour size.

metatasis were 37.1% and 46.6% for adults and 18.4% both times for children ($p = 0.008$).

Cox-regression analyses for patient-, tumour- and treatment related factors with HRs and corresponding 95%CIs are visible in Table 2. Large (>10 cm) synovial sarcomas were associated with a worse outcome on univariate analysis ($p < 0.005$). "High-risk" patients with deeply located, high grade tumours exceeding 10 cm in size had a significantly worse prognosis ($p = 0.030$) with a CSS of 46.7% at 5 and 15.6% at 10 years.

In multivariate Cox-regression analysis calculated without initially metastatic patients, large tumour size ($p < 0.005$) and advanced patient age ($p = 0.024$) proved to be independent negative prognostic factors regarding CSS (Table 3), irrespective of tumour depth and site.

We furthermore investigated the relationship between age and tumour size (Fig. 3) and found that there was a tendency for small tumours to be associated with a better outcome, confirming our results.

Discussion

In this retrospective analysis, clinical, pathological and treatment-related features of 248 synovial sarcoma patients were analysed. Patients with a prior unplanned excision of their synovial sarcoma had a significantly longer median duration of symptoms as compared to directly referred patients. Small synovial sarcomas were independently associated with a better prognosis, irrespective of patient age, history of prior unplanned excision, tumour size, anatomical location or administration of adjuvant CTX.

Several studies have been performed over the years, investigating clinical features and their influence on the prognosis of patients with synovial sarcoma (Table 4). Unlike "typical" STS whose incidence increases with age and peaks in the 5th decade of life, synovial sarcomas tend to occur in young and middle-aged adults [15]. Consistent with the literature, the mean patient age in our cohort was 37.0 years, including 43 paediatric cases [9,16]. Moreover, synovial sarcomas cause a wide range of symptoms, including palpable lumps, painful masses, motor or sensory disturbance, indolent swellings or pain without any identifiable bump [17,18]. Thus, the mean duration of symptoms before diagnosis can be rather long, ranging from 6 months to 2.5 years, or in our case one patient who had symptoms for 20 years [18,19].

The reason for the long delay in diagnosis is likely to be multifactorial including patient, doctor and hospital delay, coupled with

Table 2
Univariate Cox-regression analysis for cancer-specific mortality in 223 patients with localised synovial sarcoma.

		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Gender	Male	1			0.242
	Female	0.744	0.453	1.221	
Age (continuous)	1.028	1.013	1.043		**<0.005**
Duration of symptoms	< 1 year	1			0.889
	> 1 year	0.962	0.556	1.664	
Unplanned excisions	No	1			0.245
	Yes	0.741	0.446	1.229	
Location	Superfical	1			0.140
	Deep	1.703	0.839	3.458	
Side	Left	1			0.212
	Right	0.729	0.443	1.197	
Site	Upper limbs	1			0.743
	Lower limbs	1.164	0.650	2.085	0.610
	Trunk	0.796	0.230	2.753	0.719
Grade	G1	1			**0.047**
	G2	2.739	0.373	20.120	0.322
	G3	4.804	0.647	35.671	0.125
Tumour size (continuous)		1.126	1.069	1.186	**<0.005**
Stage	I	1			**0.002**
	IIA	1.244	0.158	9.784	0.836
	IIB	3.244	0.439	23.989	0.249
	III	4.981	0.664	37.387	0.118
High risk (G3, >10 cm, deep)	No	1			**0.030**
	Yes	2.566	1.093	6.022	
Amputation	No	1			0.061
	Yes	1.735	0.975	3.087	

Bold figures show those with significance (ie p<0.05).

Table 3
Multivariate Cox regression analysis regarding cancer-specific survival in 223 synovial sarcoma patients with localised disease.

		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Age (continuous)		1.019	1.003	1.036	**0.024**
Tumour size (continuous)		1.118	1.054	1.186	**<0.005**
Location	Superficial	1			0.483
	Deep	1.331	0.599	2.956	
Site	Upper Limb	1			0.607
	Lower Limb	1.760	0.383	8.095	
	Trunk	2.008	0.477	8.453	

Bold figures show those with significance (ie p<0.05).

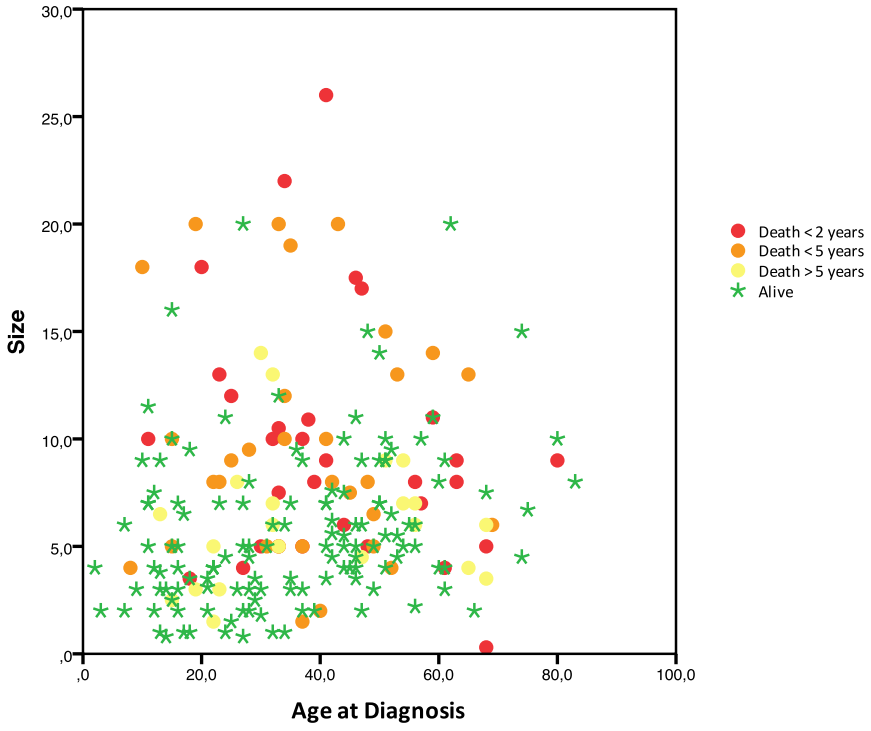

Fig. 3. Scatterplot showing correlation between tumour size and patient age.

an even lower recognition of the wide range of symptoms that synovial sarcomas can present with compared to conventional soft tissue sarcomas [20]. Having said that, the median size of the synovial sarcomas in this series was 6 cm which is considerably less that reported for other STS treated at our institution over a similar time period (9.9 cm) [21].

Unplanned excisions in any soft tissue sarcoma are associated with a high risk of residual disease and development of local recurrence [22]. In those 97 patients in our cohort with prior unplanned excision, the prognosis was not significantly impaired, probably because all of these patients underwent a further wide excision. Interestingly, symptoms had been present significantly longer in these patients, compared to the other patients, suggesting that tumours had increased slowly over a longer time period and thus had been erroneously judged as benign lesions. However, unplanned excisions in general – and especially in synovial sarcoma – are associated with an increased likelihood of residual tumour tissue [22,23].

Following treatment, 12.9% of patients developed LRs during follow up in our cohort, which is lower than local failure rates reported in the literature, which range between 15% and 38% [5,9]. We have shown however the clear association of local recurrence with closer margins, despite the fact that most patients with large tumours and anything less than a wide margin were offered radiotherapy. We did note however that of the 32 patients who developed LR, 16 (50%) subsequently developed metastases at a median time of 1.8 years and of these patients 13 subsequently died. This paper cannot resolve the 'thorny' issue of whether local recurrence is an independent factor for subsequent metastatic disease but these figures are clearly a cause for concern and confirm that anyone who has had a local recurrence must be carefully followed up due to the increased risk of subsequent metastases developing.

The 5- and 10-year CSS rates for patients with localised disease undergoing curative surgery were 78.1% and 60.3%, respectively. Significantly better CSS rates emerged for paediatric patients in comparison to adults, with 5- and 10-year CSS rates being 89.0% and 78.2%. Our results are better than those reported in a study comprising 111 synovial sarcoma patients between 4 and 22 years of age, with 5- and 10-year overall-survival (OS) rates of 73% and 65%, respectively [24]. The discrepancy in prognosis may be related to the fact that we looked at CSS in paediatric patients only, whilst *Stanelle* et al. calculated OS rates only and additionally included young adults into their young patient group [24]. The slowly but constantly decreasing OS rate with ongoing age has also been

Table 4
Short summary of studies dealing with prognostic factors in synovial sarcoma.

Study	Patients and Methods	Results
Cadman, N.L. 1965 Cancer [18]	134 patients (81 male, 53 female) Mean age: 32.8 years (0.7–72 years)	– Mean duration of symptoms 2.5 years – Mean time to death (from diagnosis) 6.5 years
Oda, Y. 1993 Am J Surg Pathol [33]	56 patients	– Large tumour size, age > 20 years, high grade, high AJCC-stage associated with poor prognosis in univariate analysis – AJCC-stage only significant prognostic factor in multivariate analysis
Bergh, P. 1999 Cancer [19]	121 patients (66 male, 55 female) Mean age: 39 years	– LR in 31% of patients (n = 38), predominantly following UE – Mean follow-up of 9.8 years – 5-year and 10-year OS rates of 60% and 50%, respectively – Independent poor prognostic factors regarding MFS: adult age, high-grade tumours – DSS influenced by adult age, large tumour size, high-grade lesions, LR – 88% DFS in low-risk group as compared with 18% for high-risk group (p < 0.001)
Spillane, A.J. 2000 J Clin Oncol [5]	150 patients Mean age: 30 years	– 5-year OS rate of 57% – Age > 20 years and LR was poor prognostic factor – Size trend strongest poor prognostic indicator
De Silva, M.V.C. 2003 Sarcoma [34]	53 patients with synovial sarcoma (compared with 56 STS patients)	– Synovial sarcoma-patients had pain 12-times more often than patients with other types of STS (p < 0.001) – Presence of pain not associated with impaired outcome in synovial sarcoma patients
Ferrari, A. 2004 Cancer [9]	271 patients Median age: 32 years (range: 5–87 years)	– 5-year EFS of 37% – 16 patients (6%) metastatic spread at time of diagnosis – histological subtype, tumour site and especially tumour size associated with OS – CTX more often in children than in adults – MFS of 40% for patients without CTX as compared to 60% for patients receiving CTX – Greatest benefit of CTX for patients > 17 years with tumours > 5 cm
Chotel, F. 2008 J Bone Joint Surg (Br) [12]	35 paediatric patients Mean age: 12.3 years (range: 3–16 years)	– 75% of tumours in lower limbs, 14% in upper limbs, 11% in trunk – Mean tumour size of 6 cm (range: 1–18 cm) – Mean duration of symptoms 98 weeks (range: 0–362) – Tumours of knee/elbow associated with longer symptom duration + doctor delay – 100% adequate surgical margins – CTX in 19 patients – 5-year survival-rate 88%
Palmerini, E. 2009 Cancer [16]	250 patients (122 male, 128 female) Mean age: 37 years	– 71% of tumours in lower limbs, 16% in upper limbs, 13% in the trunk – 46 patients (18%) with primary metastases – 24% of patients underwent amputation – Adequate resection margins in 88% – 76% 5-year survival-rate for patients with localised disease (thus surgery), 10% for patients with primary metastasis (p = 0.001) – 5-year EFS 58% – Independent prognostic factors for EFS: age, size, RTX, histological subtype
Stanelle, E.J. 2013 Ann Surg Oncol [24]	111 patients (66 male, 45 female) Median age: 15.4 years (range: 4–22 years)	– 5-year OS rate 73% – 10-year OS rate 65% – Small tumour size, superficial location, no bony or neurovascular invasion and tumours of upper extremity associated with better OS in univariate analysis – Tumour size only independent prognostic factor (p = 0.02)
Choi, E.S. 2015 Clinics in Orthopedic Surgery [22]	90 patients (56 male, 34 female) Mean age: 32.7 years (range: 5–80 years)	– Longer duration of symptoms, smaller tumour size, superficial location in UE group – No difference in LRFS (p = 0.335), MFS (p = 0.444) or DSS (p = 0.159) between directly referred patients and those with prior UE
Vlenterie, M. 2015 Br J Cancer [25]	613 patients; 54 children, 148 TYAs, 204 adults, 55 elderly	– Mean 5-year OS 89% (children), 73% (TYAs), 54% (adults), 43% (elderly) – Type of treatment had no effect on OS in univariate analysis – Multivariate analysis: Localisation of metastasis and performance status independent prognostic factors for OS
Scheer, M. 2016 Pediatr Blood Cancer [35]	296 patients < 21 years (mean age: 16.7 years); 29 with distant metastasis	– 5-year EFS 26% and 5-year OS 30% for metastatic patients – Worse prognosis when osseous or multiple bilateral lung metastases – Better survival following adequate local treatment and CTX for metastases
Brennan, B. 2016 Clin Sarcoma Res [26]	1318 patients (690 male, 628 female); 182 patients < 20 years	– Similar clinical presentation between children/TYA and adults – Advanced age, female sex, non-extremity tumour location and poor socioeconomic status associated with worse prognosis

LRFS (local recurrence free survival), MFS (metastasis free survival), DSS (disease specific survival), EFS (event-free survival), UE (unplanned excision), OS (overall survival), TYA (teens and young adults), CTX (chemotherapy).

observed by *Vlenterie* et al. in a study evaluating the influence of age on prognosis. They reported a mean 5-year OS being 89% in children, 73% in teens and young adults, 54% in adults and 43% in elderly patients [25]. Moreover, a recent study from the English cancer registry reported improved survival in younger patients but did not include prognostic factors such as size or stage of the tumour at presentation but interestingly suggested that socioeconomic deprivation may have a role in worse outcomes [26].

The prognostic significance of tumour size is consistently reported in the literature [5,27]. Thus, unsurprisingly, we identified large tumour size as an independent negative prognostic factor in our cohort. However, there was no significant difference in tumour size between paediatric patients and adults. *Ferrari* et al. suggested that the prognostic significance of tumour size was related to the patients' body size [28]. In small individuals, large tumours have a stronger negative impact on prognosis than equally sized tumours

would have in tall patients [28]. We were not able to confirm this from our data. Nevertheless, the two independent negative prognostic factors identified in the present study were large tumour size and advanced patient age.

Administration of adjuvant ifosfamide/doxorubicin-based CTX is recommended in children with synovial sarcoma, as these tumours rather resemble paediatric rhabdomyosarcoma than other STS-subtypes regarding response to CTX [29,30]. In the present cohort, however, adjuvant ifosfamide/doxorubicin-based CTX was predominantly used in "high-risk" patients, thus we could not investigate the influence of CTX on CCS. Interestingly, studies carried out by the EORTC have failed to find any benefit for chemotherapy in young adults with advanced disease [31].

Nevertheless, better survival-rates for children in comparison to adult patients have already been observed in Ewing's sarcoma [32]. Likewise, in a single-centre study including 250 patients with synovial sarcoma, adult age was identified as an independent negative prognostic factor regarding event-free survival [16]. Notably, authors used different age groups to our study. In our cohort, young patient age was associated with a significantly better CSS in the univariate setting. Likewise in the multivariate analysis, the significance prevailed, together with tumour size as independent prognostic factors regarding CSS.

This paper does have some limitations as will any retrospective study. In patients treated following an inadvertent excision it was not aways possible to estimate the original tumour size which has handicapped some analyses. Furthermore although patients were treated with a consistent protocol throughout the series, some patients, particularly those with perceived aggressive disease may have had additional therapy such as chemotherapy or may have had excisions with close margins or even amputations. This may explain why patients who had amputations did worse – because they already had worse disease.

In conclusion, by retrospectively analysing patients with synovial sarcoma treated at our institution, we could demonstrate that large tumour size and advanced patient age are independent negative prognostic factors for CSS, irrespective of anatomical tumour location and tumour location relative to the fascia.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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