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Review

Synovial sarcoma of children and adolescents: The prognostic role of axial sites

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ABSTRACT

Background: The outcome of patients with non-extremity synovial sarcoma (SS) is generally worse than that of patients with limb tumours.
Methods: The present study analysed a series of 115 consecutive SS patients treated in Italian paediatric protocols (period 1979–2005), mainly focusing on the 30 cases arising from 'axial' sites (16 head–neck, 8 trunk, 4 lung-pleura and 2 retroperitoneum).
Results: Initial gross resection was achieved in 40% of axial cases and in 80% of limb SS ($p < 0.0001$). Five-year EFS and overall survival (OS) were, respectively, 43.3% and 55.1% for axial SS, and 69.6% ($p = 0.0068$) and 84.0% ($p = 0.0004$) for extremity SS. Local progression/recurrence was the cause of treatment failure in 75% of relapsing patients axial disease.
Conclusions: Our findings emphasise that children and adolescents with SS originating at non-extremity locations have a worse prognosis than those with limb SS. Tumour site should be considered when defining a risk-adapted treatment strategy for SS.

1. Introduction

Synovial sarcoma (SS) is one of the most common malignant soft tissue tumours, accounting for about 8% of all soft tissue sarcomas. It is reportedly the most frequent non-rhabdomyosarcomatous soft tissue sarcoma in children and adolescents, with around 30% of cases occurring in patients under 20 years old.[1] SS is a clinically, morphologically and genetically

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distinct sarcoma, characterised by a specific chromosomal translocation *t*(X;18) (p11;q11), but, as with most soft tissue sarcomas, its pathogenesis remains unknown.[2] Despite its name, SS does not arise from synovial tissues. It can occur anywhere in the body and features a local invasiveness and a propensity to metastasize. Although the most common clinical presentation is a slow-growing mass in the soft tissues of the lower extremities, especially around the knee and ankle (associated with joints, tendons and bursal structures), sites of origin other than the extremities are more common than generally believed. SS can arise in the head and neck,[3–6] in the chest and abdominal wall,[7] in the retroperitoneum[8] and mediastinum,[9,10] in the lung and pleura,[11–16] and at other visceral locations[17–22] without joints and tendons, suggesting an origin from pluripotential mesenchymal cells capable of partial or aberrant epithelial differentiation.

When SS develop at these less common sites, it is often diagnosed late or not at all, and its treatment may be more of a challenge, particularly as concerns local therapies: resection with clear histological margins (still the keystone of treatment) is usually more difficult to achieve, and full-dose radiotherapy may also be more difficult to administer. The outcome of patients with non-extremity SS is consequently generally worse than that of patients with limb tumours.[1,23–28]

The aim of the present study was to analyse clinical findings, treatment modalities and final outcome in a large series of SS of children and adolescents, focusing mainly on the subset of patients with tumours arising from 'axial' sites to see whether the treatment strategies defined by current clinical protocols need to be intensified for this group of patients.

2. Materials and methods

The study concerned a series of 115 consecutive, previously-untreated patients with a diagnosis of SS treated in Italian paediatric protocols between 1979 and 2005. Sixty-four patients were prospectively enrolled in the national protocols coordinated by the Italian Cooperative Group (ICG) for paediatric Soft Tissue Sarcoma (now the Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee – AIEOP-STSC): 3 in the RMS'79, 16 in the RMS'88 and 45 in the RMS'96 protocols; 46 patients were treated at the Istituto Nazionale Tumori (INT) in Milan, before 1996 (when the INT joined the national protocols); 5 were treated at AIEOP centres using other protocols.

Full details of clinical data, treatment modalities and outcome were available for all patients and were reviewed for this analysis. The histological slides of all patients enrolled in AIEOP protocols were reviewed by the same national pathology panel at the time of diagnosis. Cases from the INT were recently reviewed (for inclusion in previously-published studies).[26] The *t*(x;18) and SYT-SSX transcript analyses were available for 22% of all cases (which included 50% of non-extremity cases).

All patients or their guardians had given their informed consent for enrollment in studies according to the rules adopted over the years.

For this study, we defined tumours arising from truncal locations, or sites other than the extremities, as 'axial', i.e. head and neck, lung and pleura, retroperitoneum, trunk (thoracic and abdominal wall). Limb girdles (the inguinal region, hip, buttock, shoulder and axillary region) were classed as extremity sites.

2.1. Clinical grouping and treatment

At diagnosis, local tumour extent was assessed by computerised tomography (CT) and/or magnetic resonance imaging; pre-treatment investigations included chest X-ray and/or chest CT scan, abdominal ultrasound and whole-body bone scan in most cases.

Disease was staged according to the clinical tumour-nodes-metastases (TNM) system before treatment (T stage in relation to local invasiveness and tumour diameter $\leqslant$ or >5 cm),[29] and the Intergroup Rhabdomyosarcoma Study (IRS) grouping system according to the amount and the extent of residual tumour after initial surgery (group I – complete resection, group II – microscopic residual disease, group III – macroscopic residual disease, group IV – metastases at onset).[30]

Patients were treated using multi-modality approaches including surgery, chemotherapy and radiotherapy, based on the ongoing protocols at the time of diagnosis. Treatment strategies did not change substantially over the years. Primary surgery was attempted if complete, non-mutilating resection seemed feasible; if not, a biopsy was taken and chemotherapy was administered to shrink the tumour and make it more amenable to delayed surgery. Primary re-excision was recommended prior to any other treatment when microscopic residual disease was suspected, particularly in cases of inadequate surgery based on the initial clinical assumption of a benign lesion. Radiotherapy was given to patients considered at risk of local relapse due to micro- or macroscopically incomplete resection, according to the protocols in use at the time. Chemotherapy was recommended for all patients, using the different regimens adopted over the years according to the risk group, and generally included cyclophosphamide or ifosfamide, plus vincristine, anthracyclines (doxorubicin or epirubicin) and/or actinomycin-D. In patients given primary chemotherapy, response was evaluated after 3 cycles, based on the radiologically-apparent reduction in the sum of the products of the perpendicular diameters of all measurable lesions. Response was defined as: complete (CR) = complete disappearance of disease; partial (PR) = maximal tumour reduction >50%; minor (MR) = maximal reduction >25%. Stable disease, or a reduction <25% was classified as no response, whilst an increase in tumour size or the detection of new lesions was called progression (see Fig. 1).

2.2. Statistical methods

Event-free survival (EFS) and overall survival (OS) were estimated according to the Kaplan–Meier method.[31] Patients were evaluated from histological diagnosis to latest uneventful follow-up, or disease progression, relapse or death of any cause for EFS, and to death for OS. The log-rank test was used to compare the survival curves for the different subgroups of patients to establish the potential value of prognostic factors. Chi-squared tests were used to compare the frequency of cer-

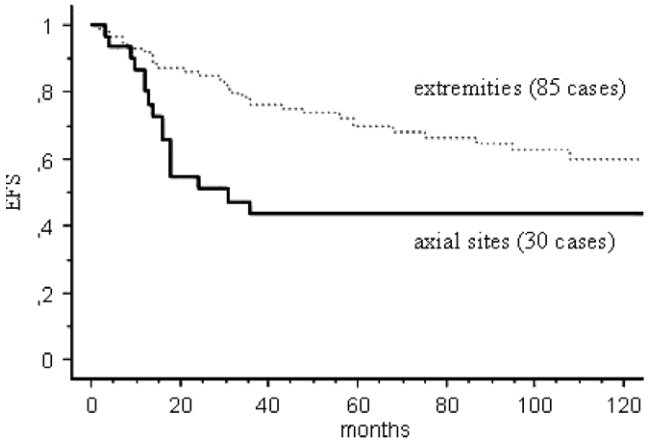

Fig. 1 – Event-free survival (EFS) in extremity and non-extremity synovial sarcoma.

tain clinical characteristics in the different patient subgroups. Patient follow-up, as at September 2007, ranged from 10 to 250 months (median 95 months) (Fig. 2).

3. Results

3.1. *Clinical findings*

The study concerned 115 patients (72 males, 43 females; age 1–20 years, median 13); 85 had tumours arising from extremities (41 distal lower limbs, 23 proximal lower limbs, 16 distal upper limbs, 5 proximal lower limbs), whilst axial regions were the site of origin in 30 cases, i.e. 16 head and neck (6 neck, 6 pharynx/parapharynx, 2 larynx, 1 maxillary sinus and 1 nasal cavity), 8 trunk (3 paraspinal, 3 thoracic wall, 2 abdominal wall), 4 lung/pleura and 2 retroperitoneum.

The first symptom of the tumour was swelling in 81% and pain in 19% of patients with extremity SS (data available for 74/85 cases); in those with axial disease (data available for 25/30 cases), it was swelling in 52% of cases and pain in 20%, whilst another 28% had specific symptoms, e.g. dysphagia or dyspnoea. The interval between symptom onset and final diagnosis ranged from 1 week and 50 months (median 2 months) for patients with limb tumour as opposed to 2 weeks–36 months (median 3 months) for patients with axial tumours.

As for histology, 12% of the limb tumours and 30% of the axial cases were poorly differentiated.

The incidence of advanced disease at diagnosis was higher in patients with axial SS than in those with limb tumours: 80% of the former had T2 tumour (versus 62% amongst limb cases), 66% had tumours larger than 5 cm (versus 50%), the median size being 7 cm (versus 5 cm). The p values were not statistically significant for the association between tumour size and local invasiveness, but a strong association emerged between tumour site and post-surgical IRS stage: 60% of axial SS were groups III–IV and initial gross resection was only achieved in 40% of them, whereas 80% of the patients with limb SS were in groups I–II and only 20% in groups III–IV ($p < 0.0001$) (Table 1).

3.2. *Treatment*

The overall treatment approach did not differ substantially for SS at different sites.

Complete surgical resection with histologically clear margins was achieved in 55 patients with extremity tumour (65%): in 14 as the initial procedure, in 29 cases after primary re-excision, performed prior to any other treatment for suspected microscopic residual disease after first resection, in 12 as delayed surgery (after chemotherapy). Six patients underwent amputation.

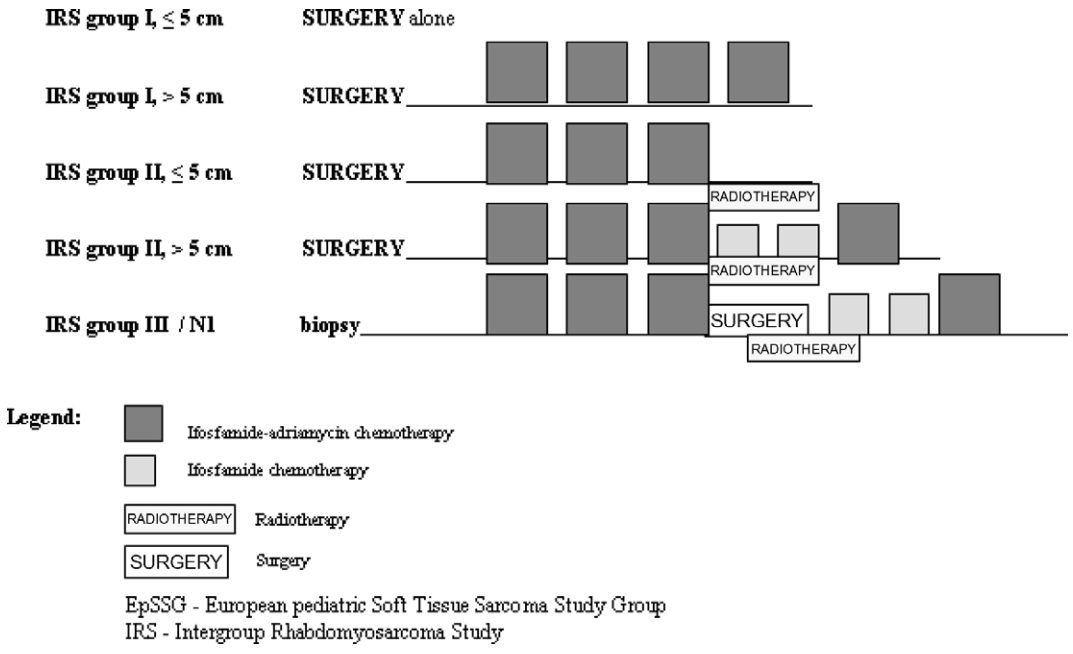

Fig. 2 – Risk-adapted treatment strategy for synovial sarcoma according to the EpSSG NRSTS 2005 protocol: stratification IRS group and tumour size.

Table 1 – Clinical characteristics, treatment modalities and survival rates, comparing extremity synovial sarcoma (SS) patients, axial SS patients and the series as a whole

	Extremity synovial sarcomas	Axial synovial sarcomas	Whole series
No. of patients	85	30	115
Gender (M/F)	53/32	19/11	72/43
Age (range/median)	1–19 years/13 years	1–20 years/12 years	1–20 years/13 years
Histology			
biph/mono/poor	37/38/10	13/8/9	50/46/19
TNM stage			
T1/T2	32/53	6/24	38/77
N1	1	1	2
M1	2	3	5 (lung metastases)
Size: range (median)	1–20 cm (5 cm)	1–22 cm (7 cm)	1–22 cm (5 cm)
⩽5 cm/>5 cm	42/43	10/20	52/63
IRS stage			
I/II/III/IV	43/25/14/3	7/5/16/2	50/30/30/5
Treatment			
Complete surgery (%)	55 (65%)	17 (57%)	72 (63%)
Radiotherapy (%)	44 (52%)	22 (73%)	66 (57%)
Chemotherapy (%)	70 (82%)	28 (93%)	98 (85%)
Outcome			
5 year EFS (%)	69.6	43.3	62.8
5 year OS (%)	84.0	55.1	76.9

M, male; F, female; biph, biphasic subtype; mono, monophasic subtype; poor, poorly differentiated subtype; TNM, tumour-nodes-metastases pre-treatment staging system; IRS, Intergroup Rhabdomyosarcoma Study post-surgical grouping system; EFS, event-free survival; OS, overall survival.

Complete surgery was achieved in 17 patients with axial tumours (57%), 7 as initial and 10 as delayed surgery.

Radiotherapy was administered to 57% of patients (52% of those with extremity SS and 73% of the axial cases): doses of 40–75 (median 50) Gy were delivered as external beam irradiation using megavoltage photon or electron beam energies and conventional fractionation (1.8–2.0 Gy daily for 5 days a week) or accelerated hyperfractionation (2 daily fractions of 1.6 Gy, at 6–8 h intervals).

Chemotherapy was given to most patients (82% of limb cases and 93% of axial cases). It was refused by parents in 6 cases and rejected by physicians in 11 cases (all small limb tumours) despite the treatment guidelines. The VAIA regimen (vincristine, adriamycin, ifosfamide and actinomycin-D) was given to 51% of patients, the VACA (vincristine, adriamycin, cyclophosphamide and actinomycin-D) to 30%, and ifosfamide and adriamycin to 10%, with the remainder receiving different ifosfamide-based regimens. In cases with measurable disease, response to chemotherapy was: 4 CR, 11 PR, 9 MR, 7 no response; the CR + PR amounted to 60% of axial cases and 33% of extremity cases.

3.3. *Outcome*

For the series as a whole, 5 year EFS and OS were 62.8% and 76.9%, respectively.

Table 2 shows the 5 year EFS according to the main clinical prognostic variables used for univariate analysis: EFS correlated closely with IRS group, T status and tumour size, and also tumour site. Five-year EFS and OS were, respectively, 69.6% and 84.0% for extremity SS and 43.3% ($p = 0.0068$) and 55.1% ($p = 0.0004$) for axial SS (see Fig. 1).

Table 2 – Five-year event-free survival (EFS) according to clinical prognostic variables (univariate analysis): the outcome of patients with axial tumours resembles that of IRS III patients, T2 patients and patients with tumours larger than 5 cm

	No.	Five year EFS	
Whole series	115	62.8%	
Histology			
Biphasic	50	70.0%	
Monophasic	46	57.9%	
Poorly diff	19	57.4%	p = NS
Age			
⩽10 years	28	71.4%	
>10 years	87	60.0%	p = NS
IRS group			
I	50	75.9%	
II	30	66.2%	
III	30	44.2%	
IV	5	0%	$p < 0.0001$
Local invasiveness			
T1	54	84.6%	
T2	61	42.7%	$p < 0.0001$
Tumour size			
⩽5 cm	52	87.8%	
>5 cm	63	41.4%	$p < 0.0001$
Tumour site[a]			
Limbs	85	69.6%	
Axial sites	30	43.3%	$p = 0.0068$

a Five year OS 84.0% for limbs and 55.1% for axial sites ($p = 0.0004$).

Table 3 – Synovial sarcoma series from the literature: comparison between extremity and non-extremity tumours

Authors	Series	Comparison between extremity and non-extremity tumours
Paediatric series		
Okcu, 2003 international paediatric multicentre study	219 pts < 20 years Five year EFS 72%, OS 80%	Non-extremity sites – 10% (15 abdomen, 6 head–neck) Five year EFS: lower extremities 73%, upper extremities 81%, abdomen 47%, head–neck 67%
Brecht, 2005 ICG-CWS paediatric cooperative group	150 pts < 18 years Only grossly-resected cases Five year EFS 77%, OS 89%	Non-extremity sites – 14% Five year OS: extremities 90%, other sites 88% → in resected cases, no main differences in outcome according to tumour sites
Adult series		
Brodsky, 1992	95 Adults	Non-extremity sites – 11% (6 trunk, 2 head–neck, 1 retroperitoneum and 1 mediastinum)
Memorial Sloan-Kettering Cancer Center, New York	Five year OS 59%	Local recurrence: 14% in extremity tumours, 50% in others
Spillane, 2000	150 Adults	Non-extremity sites – 19% (14 trunk–abdomen, 10 trunk chest, 9 head–neck, 5 retroperitoneum)
Royal Marsden Hospital, London	Five year OS 59%	Five year OS: extremities 59%, other sites 50%
Trassard, 2001	128 Adults	Non-extremity sites – 24% (10 trunk and abdomen, 7 head–neck, 14 pelvis)
French Federation of Cancer Centers Sarcoma Group	Five year DSS 63%	Five year DSS: extremities 66%, non-extremities 53% → truncal location is a significant prognostic factor in multivariate analysis
Ferrari, 2004	271 pts (both children and adults)	Non-extremity sites – 14% (17 trunk, 10 head–neck, 8 abdomen–pelvis, 4 lung–mediastinum)
Istituto Nazionale Tumori, Milan	Five year EFS 37%, OS 64%	Five year EFS: distal extremities 44%, lower extremities 41%, other sites 19%
Guillou, 2004	165 Adults	Axial sites (including also limb girdles) – 33% (15 trunk-abdominal wall, 17 internal trunk, 6 head–neck)
French Federation of Cancer Centers Sarcoma Group	Five year DSS 66%	Five year DSS and LRFS: limbs 72% and 75%, axial sites 52% and 39%
Spurrel, 2005 Royal Marsden Hospital, London	104 Adults (advanced disease) 10 year metastatic rate 81%	Non-extremity sites – 29% (10 trunk, 7 abdomen, 7 head–neck, 6 retroperitoneum) → higher percentage of axial sites when considering subset of advanced tumours

Legend: EFS, event-free survival; OS, overall survival; DSS, disease specific survival; pts, patients.

The pattern of treatment failure differed according to tumour site. Amongst limb SS (85 cases), we recorded 9 local, 3 local + metastatic and 18 metastatic relapses, a median 28 months (range 2–108) after initial diagnosis. Amongst axial SS (30 cases), there were 3 local, 9 local + metastatic and 4 metastatic relapses, after a median 16 months (range 3–36). Local progression/recurrence was seen in 40% of relapsing limb tumour patients and 75% of those with axial disease.

Amongst the patients with axial SS, 5 year EFS was 57.1% in IRS group I cases (7 cases), 20% in group II (5 cases) and 51.7% in group III (16 cases) ($p = 0.0920$); 80% in T1 (6 cases) and 34.7% in T2 tumours (24 cases) ($p = 0.0674$); 70% and 35%, respectively, for tumours $\leqslant$ (10 cases) or >5 cm (20 cases) ($p = 0.0874$); 59.5% for head–neck tumours (16 cases), 35% for trunk/retroperitoneal tumours (10 cases), 0% for lung/pleural sites (4 cases) ($p = 0.0016$). The small number of cases in these subgroup clearly limits the value of this univariate analysis.

4. Discussion

Different strategies have been developed over the years for paediatric and adult oncology protocols dealing with SS. High rates of response to chemotherapy were recorded in paediatric series, so SS came to be considered an 'RMS-like' tumour (in Europe at least) and most paediatric patients were consequently included in RMS protocols.[1,26,32–35] The European paediatric Soft Tissue Sarcoma Study Group (EpSSG) has since developed a protocol tailored to non-rhabdomyosarcoma soft tissue sarcomas, with a trial dedicated to SS, based on recently-published analyses on paediatric SS series[1,26,35,36] and data from adult studies[25–28,37,38] suggesting that the quality of surgical margins (i.e. IRS grouping) and initial tumour size are the two variables to consider in stratifying patients and defining risk-adapted therapy (with or without adjuvant chemotherapy and radiotherapy, the number of ifosfamide–doxorubicin courses, radiotherapy dosage) (see Fig. 2).[39]

In the current study, we would suggest that the outcome of SS at axial sites is so unsatisfactory that researchers should consider tumour location as a factor in patient stratification and treatment decisions.

Axial tumours account for 1 in 4 of all SS, at most, though some authors claim the percentage may be higher, particularly due to pleural or pulmonary SS cases being misdiagnosed because tumours are not systematically examined for

SS molecular markers: these authors suggest that molecular testing of SYT-SSX may be useful or even essential to accurate diagnosis in cases of suspected mesenchymal malignancies in non-extremity sites.[16]

Molecular analyses are not mandatory for diagnosis in Italian protocols and were performed in only 22% of all cases enrolled in our series, but in 50% of patients with axial tumours.

Table 3 shows that both adult and paediatric series of SS (all sites) achieved unsatisfactory survival rates for cases of axial disease; the outcome of axial and extremity SS only seemed similar in the series from the Italian and German cooperative group, which selected paediatric patients with grossly-resected tumours.[35]

Table 4 lists reports on SS at unusual sites, most of which included very few cases and confirmed a tendency for a poor outcome in non-extremity SS. The series from the French Sarcoma Group reported on 40 adults with t(x;18)-positive intrathoracic SS (77% with pleuropulmonary SS): disease-free survival was 21% at 5 years and the authors attributed this poor outcome to a combination of factors including diagnostic delay and difficulties in obtaining tumour-free margins, but also more older patients and a higher incidence of large, poorly-differentiated and high-grade tumours.[16]

In our large prospective series of paediatric SS patients, we confirmed the unsatisfactory prognosis for the roughly 25% of axial cases: treatment outcome in these patients was much the same as in IRS III patients and those with tumours >5 cm, patients considered at high risk in current protocols (and consequently given more intensive treatment). We also found that: (1) axial SS were not associated significantly more than limb tumours with diagnostic delay or large tumour size; and (2) the chances of initial gross resection were strongly influenced by tumour site (IRS group I–II patients were 80% and 40%, respectively, in limb and axial tumours). In principle, this means that the worse outcome in axial tumours relates especially to the more difficult initial resection, a suspicion confirmed by the high rate of local failure. Moreover, the difficulty in performing initial surgery caused an increase in the number of axial cases who required radiotherapy (73% versus 52%).

On the other hand, axial SS outcome was unsatisfactory in patients achieving initial gross resection too (5 year EFS was 57% for IRS group I and 20% for group II) possibly suggesting a more aggressive clinical course – and biology – of non-extremity SS. We also confirmed a higher incidence of poorly differentiated disease at axial sites. The only axial SS with a good prognosis were tumours in situ less than 5 cm in size.

Of course, grouping all non-extremity sites together is an arbitrary simplification. The group could include deep-seated disease, as in the lung/pleura or retroperitoneum (always difficult to manage surgically) and superficial sites such as certain head–neck or chest wall locations, that are sometimes easier to resect. Though ours is one of the largest reported series of paediatric SS, the rarity of this disease prevents any detailed analysis of specific tumour sites. We can nonetheless confirm that clinical behaviour was not the same at all axial sites of origin: the outcome was very poor for lung and pleural tumours, whilst head and neck cases seemed to fare rather better.

In conclusion, our findings emphasise that children and adolescents with SS originating at non-extremity locations have a worse prognosis than those with limb SS, so tumour site should be considered (as is the case for rhabdomyosarcoma) when defining a risk-adapted treatment strategy for SS. Patients with unfavourable tumour sites are likely to benefit from the most aggressive therapy, i.e. in terms of number

Table 4 – Synovial sarcoma of axial sites: published series

Authors	Series
Head–neck	
Roth, 1975	24 pts (age 10–51 years) – cervical tissues, retropharyngeal spaces – 12/21 died
Shmookler, 1982	11 cases (16–49 years) – facial tissues (i.e. cheek, parotid region), intraoral spaces
Pai, 1993	11 cases – parapharynx, pharyngeal wall, neck – 5 died
Harb, 2007	40 cases
Intrathoracic sites	
Zeren, 1995	25 Pulmonary SS (11–77 years) – 10 died, 8 alive with tumour, 4 alive without disease
Keel, 1999	6 Primary pulmonary SS (from a series of 26 sarcomas)
Aubry, 2001	5 Cases of primary pleural monophasic SS
Essary, 2001	12 SS arising in the lung (9 cases) or pleura (3) – 8 recurrences within 2 years
Okamoto, 2004	11 Primary pulmonary SS (29–81 years, median 50) – 70% recurred
Suster, 2005	15 Mediastinal SS (9 anterior, 6 posterior mediastinal) – poor outcome
Begueret, 2005	40 t(x;18)-positive intrathoracic SS (77% pleuropulmonary) Five year DFS and DSS 21% and 32% – poor outcome related to the predominance of older aged pts, large tumour size, poorly differentiated and high grade histology
Hartel, 2007	60 Primary pulmonary and mediastinal SS – pathological review
Other sites	
Shmookler, 1982	4 Retroperitoneal SS (17–57 years)
Fetsch, 1993	27 SS of the abdominal wall (8–58 years, median 23) – mortality 50%
Jun, 2004	3 SS of the kidney (26–35 years)
Billings, 2000	2 SS of the upper digestive tract – literature review: 5 cases of the proximal oesophagus
Single case reports of SS arising from heart (Nicholson, 1997), prostate (Iwasaki, 1999), liver (Holla, 2006), meninx (Sakellaridis, 2006)	

Legend: SS, synovial sarcoma; DFS, disease-free survival; DSS, disease-specific survival; pts, patients.

of chemotherapy cycles. For instance, the current EpSSG protocol considers tumour size and IRS group to stratify patients as: low-risk (group I, size $\leqslant$5 cm: no adjuvant chemotherapy recommended), intermediate risk (group I, size >5 cm; group II, size $\leqslant$5 cm: 3–4 courses of chemotherapy) and high-risk (group II, size >5 cm; group III: 6 courses of chemotherapy) (see Fig. 2).[39] If we were to consider all axial SS as high-risk, 9/30 patients in our series would move from the low- (2 cases) and intermediate- (7 cases) risk groups to the high-risk group.

Conflict of interest statement

None declared.

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