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Original Research

Clinical features and outcomes of young patients with epithelioid sarcoma: an analysis from the Children's Oncology Group and the European paediatric soft tissue Sarcoma Study Group prospective clinical trials

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KEYWORDS
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Abstract ***Background:*** Data on the clinical features, optimal treatment and outcomes of paediatric patients with epithelioid sarcoma (ES) are limited and mostly retrospective.
Methods: A subset analysis of ES patients < 30 years of age enrolled on two international prospective clinical trials conducted between 7/2005 and 11/2015 was performed. Risk-adapted therapy was based on tumour diameter, histologic grade, extent of surgery and presence/absence of metastases and included surgery ± radiotherapy for all patients with the addition of ifosfamide/doxorubicin chemotherapy for intermediate-/high-risk patients. Response to therapy, event-free and overall survival and pattern and predictors of treatment failure were evaluated.
Results: Sixty-three ES patients (median age 13.1 years, 52% male) were eligible. Clinical features included the following: 68% extremity, median tumour diameter 3.5 cm, 56% high histologic grade, 14% nodal metastases, 14% distant metastases. Thirty-four low-risk patients underwent surgery (n = 30) or surgery/radiotherapy (n = 4); 16 intermediate-risk and 13 high-risk patients received chemotherapy ± surgery ± radiotherapy. Partial response was observed in 11/22 (50%) patients receiving neoadjuvant therapy. Events were local recurrence (n = 10) and distant recurrence (n = 15); estimated 5-year survival was 86.4%, 63.5% and 0%, respectively, for low-, intermediate- and high-risk patients. Locoregional nodal involvement, invasive tumour, high grade and lesser extent of resection predicted event-free survival in patients without metastases.
Conclusions: Most low-risk ES patients who have undergone an adequate resection fare well without adjuvant therapy. Large tumour size, high histologic grade, tumour invasiveness, inadequate tumour resection and metastatic disease predict poorer outcomes in higher risk ES patients, for whom more effective therapies are needed.
Clinical trial registration: COG ARST0332: ClinicalTrials.gov Identifier NCT00346164, EpSSG NRSTS 2005: European Union Drug Regulating Authorities Clinical Trials No. 2005-001139-31.

1. Introduction

Epithelioid sarcoma (ES) is an aggressive neoplasm of uncertain cellular origin characterized by expression of both mesenchymal and epithelial markers. Over 90% fail to express the *SMARCB1/INI1* tumour-suppressor gene product, reflecting deletion or inactivation of this gene located at 22q11.23 [1,2]. Although the median age at presentation of ES is 30 years, it is proportionally more common in young patients, accounting for about 2% of paediatric soft-tissue sarcomas [3]. Paediatric oncologists consider ES among the large and heterogeneous group of non-rhabdomyosarcoma soft-tissue sarcomas (NRSTSs) that differ from rhabdomyosarcoma (RMS) by their relative insensitivity to chemotherapy and radiotherapy [4,5].

The rarity of ES in both paediatric and adult populations limits the available data on its natural history and treatment, most of which derives from retrospective case series [6–11]. More recently, both the North American Children's Oncology Group (COG) and the European paediatric Soft tissue sarcoma Study Group (EpSSG) included ES in prospective NRSTS clinical trials. In both trials, a risk-adapted treatment program was defined as per features previously determined to predict outcome in paediatric NRSTS: extent of disease, histologic grade and size of the primary tumour and extent of surgical resection. The current analysis pools data from these two prospective clinical trials to assess clinical features and outcomes of young patients with ES and to identify predictors of treatment failure.

2. Materials and methods

Patients under 30 years of age with newly diagnosed ES who enrolled on one of two prospective European and North American clinical trials (EpSSG NRSTS2005, 7/2005-11/2015 or COG ARST0332, 2/2007-2/2012) were eligible for this subset analysis. All participating centres obtained institutional ethics board approval as per the rules of the treating group, and written consent for treatment and data use was obtained from parents/guardians and/or patients according to local research ethics requirements.

Centralized pathology review by expert paediatric soft tissue pathologists confirmed the diagnosis in all cases as per the 2002 World Health Organization (WHO) criteria [12]. Although loss of INI1 staining was not mentioned in the 2002 WHO guidelines, the presence or absence of INI1 staining was recorded for cases in which it was performed. Histologic grade was defined by FNCLCC (Fédération Nationale des Centres de

Lutte Contre le Cancer) criteria for all patients [13], but the COG study used the POG (Pediatric Oncology Group) grading system for treatment assignment [14]. Central review of operative notes, pathology reports and imaging studies and reports defined the tumour size, sites of disease and extent of surgery by Intergroup Rhabdomyosarcoma Study (IRS) system criteria [15]. Extremity tumours were divided into proximal (shoulder to elbow, buttock to knee) and distal (forearm to finger, lower leg to toe) subsets.

Table 1 shows the treatment assignment specifications for both studies, which were similar. Regional lymph node sampling was mandatory in the COG study but was recommended only for patients with clinically or radiographically suspicious regional lymph nodes in the EpSSG study. The COG study recommended resection of metastases ± radiotherapy for unresectable disease at the end of therapy; the EpSSG study made no recommendations regarding management of metastases.

For this analysis, patients were divided into low-, intermediate- and high-risk groups as per the treatment administered. Low-risk patients underwent surgery ± radiotherapy and comprised predominantly those with non-metastatic, widely or marginally resected ≤5 cm tumours. The intermediate-risk group included patients with non-metastatic, high-grade and >5 cm or unresectable tumours. Those with nodal or distant metastatic disease were at high risk, regardless of tumour grade or size. Patients in both the intermediate- and high-risk groups received chemotherapy, radiotherapy and delayed surgery for any disease unresected at study entry. Both studies used of 6–7 cycles of ifosfamide (9 g/m2/cycle) and 4–5 cycles of doxorubicin (75 mg/m2/cycle), usually concomitantly depending on radiation timing.

In COG patients, response to therapy was evaluated after 4 cycles of chemotherapy and 45 Gy of radiotherapy by volumetric criteria (0.5 times the product of the 3 largest perpendicular diameters) for the primary tumour and by RECIST, version 1.1, criteria for metastases [16]. Primary tumour response was defined as complete response (CR): complete disappearance; partial response (PR): ≥64% decrease in volume; stable disease (SD): <64% decrease and <40% increase in volume or progressive disease (PD): ≥40% increase in volume. In EpSSG patients, response was assessed after 3 cycles of chemotherapy and was defined as CR: complete disappearance of all disease; PR: ≥66% decrease in tumour volume; SD: <66% decrease and <40% increase in tumour volume or PD: ≥40% increase in volume or appearance of new disease.

Patients were considered to be event-free until they developed tumour progression or recurrence, toxicity requiring removal from protocol therapy, a second cancer or died of any cause. Descriptive statistics (frequency and percentage for categorical characteristics; median and range for numerical characteristics) were used to describe the clinical and treatment features of the population. The Kaplan–Meier method was used to construct the event-free survival (EFS) and overall survival (OS) curves, with the standard error computed using the Peto–Pike method. The log-rank test was performed to compare EFS and OS distributions.

3. Results

Sixty-three patients with ES were eligible for this analysis: 29 enrolled in ARST0332 (2/2007-2/2012) and 34 enrolled in NRSTS2005 (7/2005-11/2015). Tables 1 and 2 show the treatment assignment algorithm and clinical features of the study cohort. INI1 staining in the 54 tumours tested showed loss in 47 (87%). An analysis for differences in the distribution of clinical features between patients treated by COG and EpSSG showed a statistically significant difference in the distribution of gender ($p = 0.0339$) but no significant differences in anatomic site, FNCLCC grade or lymph node status (data not shown).

Thirty-four of the 63 patients (54%) underwent a procedure to assess lymph node status at diagnosis, including sampling (n = 13), sentinel node biopsy (n = 19) or node dissection (n = 2). Nine of the 34 patients who had lymph node sampling were found to have metastatic tumour in the lymph node(s). Because it was required by the protocol, COG patients were more likely than EpSSG patients to undergo a lymph node procedure (97% vs. 18% of patients, respectively).

3.1. Low-risk patients (n = 34)

Thirty patients (48%), including 29 with tumours ≤ 5 cm and 20 with FNCLCC grade 2 tumours, had surgery only. Five events occurred in this group: 2 local recurrences, 1 metastases, 2 combined recurrences. Three patients who received no adjuvant therapy died, including 1 with local recurrence of a 1.6 cm grade 2 perineal tumors that had been widely excised before study entry. Four patients received adjuvant radiotherapy after upfront tumour resection. There were no local recurrences in this subgroup, but one of these patients (grade 3, 3.0 cm tumour) experienced a metastatic recurrence and did not survive.

Estimated 5-year EFS and OS for the low-risk cohort were 84.4% (95% CI, 66.2%–93.3%) and 86.4% (95% CI, 67.4%–94.7%), respectively. In a univariate analysis stratified by all risk factors, FNCLCC grade did not predict EFS or OS in low-risk patients overall ($p = 0.4243$ and 0.5085, respectively) or in low-risk patients treated with surgery alone ($p = 0.8971$ and 0.9146, respectively). Owing to the small number of patients with large (>5 cm) tumours, invasive (T2) tumours and IRS group II resection before study entry, it was not possible to reliably determine whether these

Table 1
COG and EpSSG treatment assignment algorithm.

COG ARST0332	**Number of Patients 29**
No adjuvant therapy	**17**
IRS group I, any size, POG grade 2	13
IRS group I, ≤5 cm, POG grade 3	4
Adjuvant radiotherapy	**1**
IRS group II, ≤5 cm, POG grade 3 (55.8 Gy)	1
Adjuvant chemotherapy + radiotherapy	**5**
IRS group I/II, >5 cm (55.8 Gy)	1
IRS group I/II, ≤5 cm, nodal metastases (55.8 Gy)[b]	1
IRS group IV, primary tumour grossly resected (55.8 Gy)[b]	3
Neoadjuvant chemotherapy + radiotherapy, delayed resection	**6**
IRS group III, any size (45 Gy plus boost based on surgical margin)[a]	4
IRS group IV, primary tumour unresected (45 Gy plus boost based on surgical margins)[a,b]	2
EpSSG NRSTS2005	**34**
No adjuvant therapy	**13**
IRS group I, ≤5 cm, any FNCLCC grade	13
Adjuvant radiotherapy	**3**
IRS group I, >5 cm, FNCLCC grade 2 (50.4 Gy)	1
IRS group II, any size, FNCLCC grade 2 (54 Gy)	1
IRS group II, ≤5 cm, FNCLCC grade 3 (54 Gy)	1
Adjuvant chemotherapy + radiotherapy	**2**
IRS group I, >5 cm, FNCLCC grade 3 (50.4 Gy)	1
IRS group II, >5 cm, FNCLCC grade 3 (54 Gy)	1
Neoadjuvant chemotherapy, delayed resection + preoperative or postoperative radiotherapy	**16**
IRS group III (50.4–59.4 Gy depending on resection timing and surgical margins)[c]	12
IRS group IV (50.4–59.4 Gy depending on resection timing and surgical margins)[c,d]	4

COG: Children's Oncology Group; EpSSG: European paediatric Soft Tissue Sarcoma Group; FNCLCC: Fédération Nationale des Centres de Luttle Contre Le Cancer; Gy: Gray; IRS: Intergroup Rhabdomyosarcoma Study; POG: Pediatric Oncology Group. The bold values represent the total number of patients in each group, with the non-bold values representing the number of patients in each subgroup.

[a] Primary tumour total dose 45 Gy following R0 resection, 55.8 Gy following R1 resection, 64.8 Gy for gross tumour.

[b] Resectable nodal and distant metastases excised at delayed surgery or at the end of therapy; unresectable metastases received 50 Gy RT when feasible.

[c] 50.4 Gy preoperatively, 50.4 Gy postoperatively following R0 resection, 54 Gy postoperatively following R1 resection, 59.4 Gy for gross tumour.

[d] Treatment of metastases per investigator choice.

clinical or treatment factors influenced outcome in low-risk patients.

3.2. Intermediate-risk patients (n = 16)

The 16 patients with non-metastatic > 5 cm or unresected tumours without nodal involvement received neoadjuvant (n = 13) or adjuvant (n = 3) therapy. Among the 13 patients who received neoadjuvant therapy (9 chemotherapy/radiotherapy, 4 chemotherapy only), 8 experienced a partial response, 4 had stable disease and 1 experienced disease progression. Seven of the 13 patients who received neoadjuvant therapy underwent delayed surgery, which achieved negative margins in all patients.

Seven of the 16 intermediate-risk patients experienced an event (5 local, 2 metastatic recurrence), yielding a 5-year EFS estimate of 55.0% (95% CI 27.9–75.6). Among the 5 patients with local progression/recurrence, 4 never underwent tumour resection and 1 had a delayed wide resection but received no radiotherapy. The median radiation dose for patients with and without local recurrence was 45.0 Gy and 50.4 Gy, respectively. Five of the 7 patients whose tumour recurred died, all after a local recurrence. Two patients are alive after pulmonary metastatic recurrence. Estimated 5-year OS for intermediate-risk patients was 63.5% (95% CI 31.5–83.6).

3.3. High-risk patients (n = 13)

Nine patients (14% of the entire patient population) had regional lymph node involvement, 5 of whom also had distant metastases. Among the 9 patients with nodal metastases, the primary tumour was located in the extremity (n = 4), viscera (n = 2), head/neck (n = 2) and body wall (n = 1), Six patients with nodal involvement had tumours > 5 cm. Formal lymph node dissection was performed in 3 patients with nodal metastases, and one underwent an incomplete nodal dissection. Four patients received radiotherapy to involved lymph nodes. Among the 4 patients without distant metastases, 1 had undergone marginal resection of the primary tumour at study entry. The remaining 3 had gross disease at study entry and received chemotherapy (2 PR, 1 SD); 2 had a delayed resection (1 wide resection, 1 marginal resection). There

Table 2
Patient characteristics (n = 63).

Characteristics	Number (%)
Age	
Median	13.1 years
Range	2.7–24.8 years
Sex	
Male	33 (52%)
Female	30 (48%)
Primary tumour site	
Head/neck	10 (16%)
Upper extremity	31 (49%)
Body wall	7 (11%)
Visceral	3 (5%)
Lower extremity	12 (19%)
Extremity tumour lcation	
Proximal	9 (21%)
Distal	34 (79%)
Locoregional lymph node involvement	
N0	54 (86%)
N1	9 (14%)
FNCLCC grade	
2	28 (44%)
3	35 (56%)
Maximal tumour diameter [a]	
Median	3.5 cm
Range	0.4–19 cm
IRS clinical group	
I	32 (51%)
II	6 (10%)
III	16 (25%)
IV	9 (14%)

FNCLCC: Fédération Nationale des Centres de Luttle Contre Le Cancer; IRS: Intergroup Rhabdomyosarcoma Study.
[a] Tumour diameter not available for 4 patients.

were no reported local or nodal recurrences in the 9 patients with nodal metastases, but 8 died after distant metastatic recurrence. The sole survivor with nodal metastases had no distant metastases at initial presentation and was alive at 1.2 years from study entry.

Nine patients (14% of the entire patient population) had distant metastases involving: lung (n = 7), distant lymph nodes (n = 3) and other sites (n = 6). Compared with those with localized disease, patients with distant metastases were more likely to have non-extremity tumours (67% vs. 26%, p = 0.02), tumours >5 cm in maximal diameter (44% vs. 30%, p = 0.40) and lymph node involvement (63% vs. 8%, p < 0.0001). Six of the 9 patients with metastases underwent gross resection of the primary tumour (4 before study entry, 2 in delayed fashion), but only 1 of these patients underwent complete resection of all metastases. Among the 5 patients with metastases whose disease was evaluable for response, 1 had a partial response, 1 had stable disease and 3 had progressive disease. All 9 patients with metastases at study entry experienced an event (1 local, 8 metastatic recurrences) at a median of 5.4 months (range 0.8–22.9 months). Only 1 patient remains alive, with persistent metastatic disease.

3.4. Response to neoadjuvant therapy

In all, 16 non-metastatic and 6 metastatic patients received neoadjuvant therapy including chemotherapy/radiotherapy (n = 16) or chemotherapy alone (n = 6). Eleven patients had a partial response (50%), 6 had stable disease (27%) and 5 had disease progression (23%). There was no evidence of a difference in response (PR vs. SD vs. PD) based on whether the neoadjuvant therapy was chemotherapy alone or combined with radiotherapy (p = 0.69). Of the 22 patients who received neoadjuvant therapy, 11 (50%) underwent gross tumour resection; 10 achieved negative margins.

3.5. Tumour recurrence

Twenty-five of the 63 patients (40%) experienced tumour progression or recurrence, which was local in 10 and distant in 15. Median time to tumour recurrence was 6.6 months (range 0.8–76.1 months). Only five patients with tumour recurrence (20%) were alive at the time of this analysis, one after local and four after metastatic recurrence. The patient with local recurrence has no evidence of disease at 25.8 months from the event. Two of the four patients with metastatic recurrence are alive with disease at 11.2 and 19.2 months, respectively, from the event; the remaining two are alive with unknown disease status at 12.3 and 33.9 months from the event, respectively.

3.6. Predictors of outcome

Median follow-up of the cohort is 57.8 months (range 8.4–107.9 months). Among the 20 patients who died, the cause of death was local tumour progression in seven and metastases in 13. At 5 years, estimated EFS and OS for the entire cohort were 60.7% (95% CI 47.2–71.8) and 63.6% (95% CI 48.8–75.2), respectively.

The presence or absence of distant metastatic disease was a strong predictor of outcome: 5-year EFS 71.3% (95% CI, 56.7.0–81.7) for localized disease vs. 0% for metastatic disease, p < 0.0001 and OS 75.0% (95% CI, 59.8–85.2) vs. 0%, p=<0.0001 (Fig. 1). Table 3 shows the impact of clinical features and treatment response on 5-year EFS and OS for patients with localized disease. Predictors of poorer EFS and OS in non-metastatic patients included invasiveness, more advanced IRS clinical group, higher FNCLCC grade and locoregional nodal involvement. Assigned risk group, which incorporated several of these prognostic factors, was also a robust predictor of 5-year overall survival (p < 0.0001).

4. Discussion

This analysis of the clinical features and outcomes of young patients with ES treated with a standardized

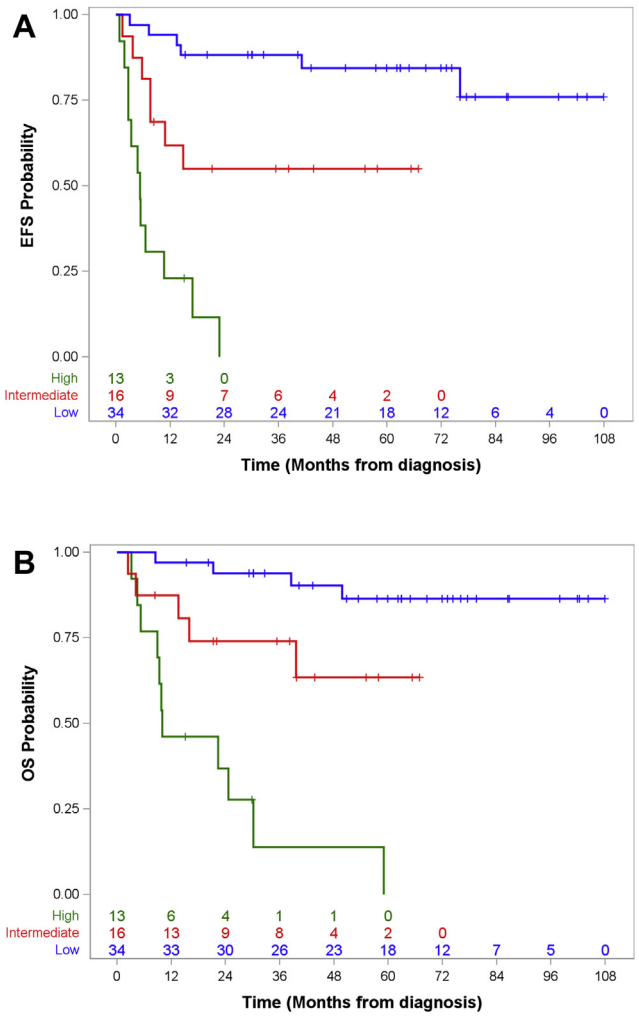

Fig. 1. Event-free and overall survival by risk group in patients with epithelioid sarcoma Panel A. Event-free survival, Panel B. Overall survival. EFS: event-free survival; OS: overall survival.

approach on prospective clinical trials demonstrates the value of international collaboration for investigating rare entities and validates prior observations from retrospective case series. Like previously published smaller retrospective case series [8,10,17], we found that paediatric ES has a slight male predominance and occurs most often in adolescents. About two-thirds of these tumours arose in the extremities, usually distally.

As in prior studies [1,2], loss of INI1 staining was very common but not universal, occurring in 87% of cases evaluated. In current practice, INI1 immunostains are used as part of the ancillary diagnosis of epithelioid sarcoma. However, this was not a part of the WHO guidelines in 2002, and indeed, there is an INI1 retention rate of 5–25% in several series which appears to be related to alterations in other components of the SWItch-Sucrose Non-Fermentable (SWI-SNF) complex [18]. Owing to these factors, data regarding INI1 expression were neither not uniformly available in our cases nor were was its loss required for diagnosis.

We found that the vast majority of patients with adequately excised small tumours can be safely treated with surgery alone. Our findings are similar to those of a previously published joint COG–EpSSG analysis that confirmed the safety of a surgery-only approach for low-risk synovial sarcoma [19], suggesting that even histologically aggressive soft-tissue sarcomas that are < 5 cm and adequately excised may not need adjuvant therapy. Despite their overall good outcome, a small handful of low-risk ES patients died of disease progression. We were unable to identify tumour features that differentiated these patients from the rest of the low-risk group, suggesting that more work is needed to identify biologic predictors of outcome that more effectively identify those who would benefit from therapy intensification.

Patients with intermediate-risk (non-metastatic, $>$ 5 cm or unresected) tumours had an EFS around 50%. Half of our patients with unresected tumours experienced a partial tumour response after neoadjuvant chemotherapy $\pm$ radiotherapy. This finding is consistent with the 43% response rate reported in a smaller retrospective paediatric case series in which only chemotherapy was given preoperatively [8]. In adults, response rates after chemotherapy alone are in the 0–15% range [11,20]. Whether the higher response rate we observed was due to more frequent use of radiotherapy in combination with chemotherapy or to differences in tumour biology in children compared with adults is unclear. Because nearly three-quarters of our neoadjuvant therapy patients received both chemotherapy and radiotherapy, we evaluated whether combination therapy produced a higher response rate than chemotherapy alone but could find no evidence of a differential response. However, we cannot definitively exclude radiotherapy as a contributor to tumour response given the small number of patients in our series. Administering radiotherapy before tumour resection carries several potential benefits, including lower prescribed doses, smaller field sizes and resection of irradiated tissue that may lower the risk of secondary neoplasia in young patients with many years to develop this treatment complication. About half of our patients with gross disease at study entry were able to undergo complete resection after neoadjuvant therapy. Therefore, combined modality neoadjuvant therapy should be considered for patients who are anticipated to require both treatment modalities, including those with initially unresectable disease.

Because all patients with >5 cm tumours received chemotherapy, we cannot definitively confirm the benefit of chemotherapy for preventing metastatic recurrence. However, the fact that distant metastases were the site of the first failure in only 2 of 16 patients (13%) with initially non-metastatic large tumours suggests a potential benefit for chemotherapy, considering that distant metastases are the most common site of recurrence and cause of death in adults who succumb to ES [6,9,11].

Table 3
Predictors of EFS and OS in patients with localized disease (n = 54).

Characteristic	#	5-year EFS (95% CI)	Log-rank test p value	5-year OS (95% CI)	Log-rank test p value
Clinical trial group					
COG	24	61.5% (38.9–77.9)	0.21	69.2% (45.7–84.1)	0.38
EpSSG	30	79.6% (60.1–90.3)		80.6% (58.6–91.7)	
Gender					
Female	28	61.2% (38.9–77.5)	0.24	68.5% (46.0–83.2)	0.18
Male	26	80.8% (59.8–91.5)		82.2% (58.7–93.1)	
Age					
1–9 years	18	77.8% (51.1–91.0)	0.62	75.4% (46.4–90.2)	0.97
10–17 years	31	68.9% (48.1–82.7)		73.7% (51.7–86.8)	
≥18 years	5	–		–	
FNCLCC grade					
2	24	91.7% (70.6–97.8)	0.01	89.8% (64.3–97.4)	0.02
3	30	54.4% (34.2–70.8)		62.8% (41.2–78.4)	
Tumour invasiveness[a]					
T1	36	86.1% (69.8–94.0)	0.0002	84.1% (65.7–93.2)	0.01
T2	17	34.3% (11.0–59.5)		52.3% (23.4–74.8)	
Maximal tumour diameter[a]					
≤5 cm	37	77.2% (59.2–88.0)	0.09	78.0% (58.8–89.0)	0.21
>5 cm	16	55.6% (28.6–75.9)		66.6% (37.2–84.7)	
Lymph node involvement [b]					
No	48	78.2% (63.0–87.7)	0.0002	83.7% (68.5–91.9)	<0.0001
Yes	4	–		–	
IRS group					
I	32	86.7% (68.1–94.8)	0.01	89.1% (69.7–96.4)	0.004
II	6	50.0% (11.1–80.4)		66.7% (19.5–90.4)	
III	16	48.6% (22.9–70.3)		48.1% (18.8–72.6)	
Treatment response[c]					
PR	10	58.3% (23.0–82.1)	0.68	51.4% (14.3–79.6)	0.93
SD	5	–		–	
Site within extremity[d]					
Distal	31	75.8% (55.3–87.8)	0.77	82.3% (62.3–92.3)	0.69
Proximal	9	88.9% (43.3–98.4)		87.5% (38.7–98.1)	

CI: confidence interval; COG: Children's Oncology Group; EFS: event-free survival; EpSSG: European paediatric Soft Tissue Sarcoma Group; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; IRS: Intergroup Rhabdomyosarcoma Study; OS: overall survival; PR: partial response; SD: stable disease.

[a] 1 patient with tumour invasiveness and maximal tumour diameter unknown.

[b] 2 patients with locoregional lymph node status unknown.

[c] 1 patient with progressive disease excluded.

[d] 40 patients with extremity tumours.

Although lymph node metastases are rare in most soft-tissue sarcomas, nodal involvement is present in 13–21% of adults with ES [21,22]. Fourteen percent of our patients had nodal involvement, a proportion similar to the largest previously published paediatric ES series [8]. The COG and EpSSG studies used a different strategy for lymph node staging. Sampling of lymph nodes was mandatory in the COG study and required only for clinical or radiographic nodal enlargement in the EpSSG study. Although the EpSSG approach could potentially underestimate (and therefore undertreat) patients with occult nodal involvement, an as yet unpublished COG analysis of lymph node metastases in NRSTSs including epithelioid sarcoma found that 19 of 20 patients with nodal involvement had radiographic evidence of lymph node metastases (the remaining patient did not have the nodal bed imaged). Based on these findings and the complete absence of nodal recurrences in our international analysis of epithelioid sarcoma, we believe that lymph node sampling is only warranted for patients with clinically or radiographically involved nodes. The optimal approach to management of nodal metastases is uncertain, although most of our patients had local control of their lymph nodes and no lymph node recurrences were observed. Unfortunately, aggressive local control of nodal metastases did not translate into better outcomes because most patients with nodal involvement died of distant metastatic disease. Regional lymph node metastases, therefore, portend a very poor prognosis, and efforts to improve systemic therapy may benefit these patients.

As described in the published literature [6,11,23], outcome was dismal for patients with distant metastases at study entry. These patients were more likely to have a non-extremity primary tumour, a tumour >5 cm in size, and lymph node metastases, and only one achieved gross resection of all sites of disease. Despite their poor survival, five of our nine metastatic patients with

measurable disease achieved stable disease or a partial response after neoadjuvant therapy, suggesting some potential for intensive chemotherapy ± radiotherapy to prevent disease progression at least in the short term. In addition to ifosfamide/doxorubicin as used in our study, others have documented the clinical benefit of gemcitabine, with or without docetaxel [24,25].

Predictors of EFS and OS in this analysis were similar to other studies of paediatric and adult patients with soft tissue sarcomas: FNCLCC grade, invasiveness, extent of resection and nodal or distant metastases [4,5,26–28]. Small retrospective case series and population dataset analyses restricted to ES have mostly documented these same prognostic factors [6,8,11,23,29]. Although using the FNCLCC system for grading epithelioid sarcoma in adults is not recommended, our finding that FNCLCC grade predicted EFS and OS in our cohort agrees with the findings of the largest published paediatric case series [8] and suggests that this system may effectively predict outcome in paediatric patients. The largest published paediatric case series also found that tumour size >5 cm did not predict outcome, a finding that was confirmed in our larger patient cohort.

Outcomes for patients with recurrent or progressive disease in our study were poor. A significant proportion of the local failures were because unresectable tumour, emphasizing the importance of surgery in the treatment of ES. Given that some patients with metastatic recurrence may survive for several years beyond the recurrence, salvage therapy aimed at eliminating metastatic disease may be a consideration in appropriate candidates.

To summarize, this joint analysis of clinical features and outcomes of prospectively treated paediatric ES patients largely confirms the findings of previously published retrospective studies. Most low-risk patients with adequately excised ≤5 cm tumours are cured with surgery alone. We documented a relatively high rate of response to chemotherapy ± radiotherapy in paediatric ES, suggesting a potentially important role for multimodality therapy in the management of patients with high-risk features including unresectable disease. Unfortunately, outcomes for these patients and those with recurrent disease continue to be poor, so more effective therapeutic approaches are needed. As our experience demonstrates, prospective clinical trials and international collaboration are feasible and hold promise for future efforts to improve outcomes for patients with rare tumours such as ES.

Conflict of interest statement

None declared.

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