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Soft tissue sarcomas in the first year of life

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ABSTRACT

Background: Soft tissue sarcomas (STS) occurring in the first year of life represent a rare entity. Challenges in delivering optimal therapy may affect the outcome in this very young population.

Methods: We searched the SEER database for records of infants less than 1 year of age, with a reported diagnosis of STS who were diagnosed from 1973 to 2006. We analysed their clinical features and survival. These patients were also compared to older patients (1–18 years old) in order to understand the differences between the two groups.

Results: The incidence rate of STS in the first year of life was 16.0 per million. As an entity, they represented 7.3% of malignancies reported in the first year of life. One fifth of these tumours (20.9%) were reported to be metastatic at diagnosis. The most common histologies were rhabdomyosarcoma ($n = 99$, 32.8%), fibrosarcoma ($n = 74$, 24.5%), malignant rhabdoid tumours ($n = 43$, 14.2%) and haemangiopericytoma ($n = 12$, 4.0%); except for rhabdomyosarcoma, the other 3 entities were very rare in older children. The 5-year survival of STS in children less than 1 year of age (62 ± 3.0%) was significantly worse than that of older children (71 ± 0.9%, $P = 0.0002$). In a multivariate model, histologic types other than fibrosarcoma and haemangiopericytoma (HR, 5.7; 95% CI, 2.28–14.20) as well as advanced stage (HR, 5.15; 95% CI, 3.28–8.10) were found to be significant adverse prognostic factors. Significantly less use of radiation was reported in infants when compared to older children ($P < 0.0001$).

Conclusion: As a group, infantile STS are associated with worse survival than STS in older children. Outcome, however, is significantly associated with histologic subtype, with infantile fibrosarcoma and infantile haemangiopericytoma having better outcomes. Avoidance of radiotherapy in this young age may contribute to worse outcomes.

1. Introduction

Paediatric soft tissue sarcomas (STS) represent about 8% of all childhood malignancies; rhabdomyosarcoma (RMS) represents approximately half of the cases, while the remainder is the heterogeneous group of the so-called "non-rhabdomyosarcoma" STS (NRSTS).[1,2]

STS may occur at any age. In the paediatric group, STS are widely distributed from newborns to adolescents. The epidemiological pattern of the different STS subtypes varies with

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age; likewise, the clinical behaviour of a given subtype is not always uniform across age groups. In particular, infants seem to represent a peculiar subset; specific entities such as infantile fibrosarcoma (IFS) and malignant rhabdoid tumours (MRT) have their incidence peak in the first year of life,[3,4] an age group in which RMS also has unique clinical findings and outcome.[5] The natural history of STS in infants may be different from that in older children due to differences in tumour biology,[6] but also due to differences related to the host. Infants are particularly vulnerable to the acute and late effects of therapy,[7] and developmental differences in drug metabolism represent a major challenge in the appropriate use of chemotherapeutic agents.[8,9] In comparison to older children, the management of patients during the first year of life is therefore particularly difficult; tailored treatments and careful monitoring are necessary, and chemotherapy dose reduction and restricted use of radiotherapy are common practices.

To better characterise the clinical characteristics and outcome of STS occurring in patients under one year of life and their distinctive features from older children, we performed an analysis of all STS cases (occurring in 0–18 year-olds) registered in the Surveillance, Epidemiology, and End Results (SEER) public-access database collected from various geographic areas in the United States.

2. Patients and methods

2.1. Data source and study population

The clinical and outcome data of infants (<1 year old) with a reported diagnosis of STS were obtained from the SEER 17 registries (http://seer.cancer.gov/data/).[10] We used the "case listing session" of the SEER*Stat 6.5.2 program to generate a matrix of all individuals diagnosed with STS in the database. A selection query was designed to retrieve data on tumours based on the International Classification of Childhood Cancer, version 3 (ICCC-3)[11] with a selection criteria of "IX: soft tissue and other extraosseous sarcomas" and "VI (a2): rhabdoid renal tumours". The inclusion of rhabdoid renal tumours was based on the assumption that these tumours have similar behaviour, age distribution and outcome to rhabdoid tumours arising from other sites.[3] The query was restricted to patients who were actively followed and who had microscopic confirmation of their tumours. The "frequency session" of the SEER*Stat software was used to calculate the frequency in older children (1–18 years old) and their clinical features. Using this session, the total number of patients registered in the SEER database can be retrieved. The "rate session" of the SEER9 database was used to calculate the incidence of STS in infants and older patients. This session calculates the number of cancer (STS in this study) per 100,000 persons (modifiable) per year. The denominator is represented by the general population census in the areas covered by the SEER registries.

2.2. Data analysis

The resulting matrix from SEER*Stat was transferred to MedCalc for Windows version 10.4.0.0 (MedCalc Software, Mariakerke, Belgium) for statistical calculations. Tumour primary sites were grouped into head and neck, extremities, trunk (including thorax, abdomen and pelvis), genito-urinary tract (including the kidneys) and others and not otherwise specified locations (others/NOS). In the SEER staging system, localised stage refers to an invasive neoplasm confined entirely to the organ of origin; regional stage refers to a neoplasm that has extended beyond the limits of the organ of origin directly into surrounding organs or tissues, has spread to regional lymph nodes by way of the lymphatic system or both and distant stage refers to a neoplasm that has spread to parts of the body remote from the primary tumour either by direct extension or by discontinuous metastasis to distant organs and tissues or via the lymphatic system to distant lymph nodes.

Death from any cause was chosen as an end-point in survival analyses. Overall survival (OS) estimates were calculated using the Kaplan–Meier method; the log-rank test was used to compare survival curves. Survival estimates were presented followed by standard errors (SE). Cox-proportional hazards regression was used to conduct the multivariate analysis. The chi-square test was used to compare categorical variables in the study.

3. Results

3.1. Clinical characteristics of STS in infants

We identified 302 infants with STS who were diagnosed from 1973 to 2006. As a group, STS ranked as the fifth most common malignancy in infants, representing 7.3% of all tumours diagnosed below the age of 1 year and registered in the open-access SEER database. In older children (1–18 years old), STS was the fourth most common malignancy, representing 7.5% of tumours (Table 1). The annual incidence rate of STS in the first year of life was 16.0 per million. The incidence was lower in older children (1–4 years, 9.4 per million; 5–9 years, 8.0 per million and 10–14 years, 10.6 per million).

Table 2 summarises the clinical characteristics of the 302 infants with STS, compared with those of 3316 older children (1–18 years old) with STS. In patients under 1 year of age, the trunk (25.5%) and the head and neck region (23.5%) were the

Table 1 – Paediatric cases registered in the SEER database (1973–2006).

	Less than 1 year old		1–18 year old	
	N	(%)	N	(%)
Neuroblastoma	979	(23.8)	1774	(4.0)
Leukaemia	639	(15.6)	12,721	(28.6)
CNS tumours	531	(12.9)	8004	(18.0)
Retinoblastoma	378	(9.2)	644	(1.4)
Soft tissue sarcomas	302	(7.3)	3316	(7.5)
Nephroblastoma	291	(7.1)	1780	(4.0)
Extracranial GCT	293	(7.1)	1740	(3.9)
Hepatic tumours	188	(4.6)	440	(1.0)
Lymphoma	124	(3.0)	6390	(14.4)
Bone tumours	9	(0.2)	2643	(5.9)
Others	375	(9.1)	5026	(11.3)
Total	4109		44,478	

Table 2 – Patient characteristics and treatment modalities in infants and older children with STS.

Variable	Less than 1 year old		1–18 years old		P
	N	(%)	N	(%)	
Total	302		3316		
Sex					
Male	171	(56.6)	1809	(54.6)	0.53
Female	131	(43.4)	1507	(45.4)	
Race					
White	246	(81.5)	2556	(77.1)	0.22
Black	35	(11.6)	469	(14.1)	
Other	21	(7.0)	291	(8.8)	
Site					
Head and neck	71	(23.5)	800	(24.1)	<0.0001
Extremity	56	(18.5)	1014	(30.6)	
Trunk[a]	77	(25.5)	806	(24.3)	
Genitourinary	59	(19.5)	348	(10.5)	
Others/NOS	39	(12.9)	348	(10.5)	
Stage					
Localised	112	(37.1)	1381	(41.6)	0.58
Regional	78	(25.8)	931	(28.1)	
Distant	63	(20.9)	656	(19.8)	
Unstaged	49	(16.2)	348	(10.5)	
Radiation					
Given	55	(18.2)	1521	(45.9)	<0.0001
None	247	(81.8)	1795	(54.1)	
Surgery					
Performed	230	(76.2)	2487	(75.0)	0.71
Not performed	72	(23.8)	829	(25.0)	

NOS, not otherwise specified.
[a] Including thorax, abdomen and pelvis.

Table 3 – Histotypes of soft tissue sarcomas diagnosed in infants less than 1 year old and older children.

Variable	Less than 1 year old		1–18 years old	
	N	(%)	N	(%)
RMS	99	(32.8)	1416	(42.7)
FS	74	(24.5)	146	(4.4)
MRT	43	(14.2)	41	(1.2)
HPC	12	(4.0)	19	(0.6)
DFS	9	(3.0)	260	(7.8)
ESFT	9	(3.0)	187	(5.6)
MFH	5	(1.7)	148	(4.5)
MPNST	4	(1.3)	122	(3.7)
SS	0	(0.0)	239	(7.2)
ASPS	0	(0.0)	37	(1.1)
NOS	15	(5.0)	154	(4.6)
Others	32	(10.6)	547	(16.5)

RMS, rhabdomyosarcomal; FS, fibrosarcoma; MRT, malignant rhabdoid tumour; HPC, haemangiopericytoma; DFS, dermatofibrosarcomal ESFT, Ewing sarcoma family of tumours; MFH, malignant fibrous histioctyomal; MPNST, malignant peripheral nerve sheath tumour; SS, synovial sarcoma; ASPS, alveolar soft part sarcoma; NOS, not otherwise specified.

most common primary sites; these percentages were similar to those seen in older children. However, infants had a higher proportion of genito-urinary tumours and a lower occurrence of extremity primaries. Gender, race and stage distribution were similar in the two age groups. While almost three-quarters of infants underwent surgery, only 18.2% received radiotherapy, compared to 45.9% of older children ($P < 0.0001$).

In infants, RMS represented one third of all cases of STS (32.8%), compared to 42.7% of STS in older children. The 3 most common NRSTS in infants were fibrosarcoma (24.5%), MRT (14.2%) and haemangiopericytoma (4%); these types represented 4.4%, 1.2% and 0.6% of STS, respectively, in older children (Table 3). In addition, the following cases were reported in infants: Ewing sarcoma family of tumours (ESFT, $n = 9$), dermatofibrosarcoma (DFS, $n = 9$), malignant fibrous histiocytoma (MFH, $n = 5$) and malignant peripheral nerve sheath tumour ($n = 4$). Fifteen tumours (5%) were not specified (ICD-O-3, 8800/3: sarcoma, not otherwise specified [NOS]). The remaining 32 tumours fell under 18 different categories. There were no records of synovial sarcoma or alveolar soft part sarcoma; these 2 types represented 7.2% and 1.1% of STS in older children, respectively.

In infants, there was an association between site and histology (Fig. 1). RMS was the most common tumour at all sites, except for the extremities, where fibrosarcoma was the predominant subtype (41% of limb tumours).

3.2. Clinical features of the different histotypes

Among the 99 cases of infantile RMS, embryonal histology was the most common subtype ($n = 59$, 59.6%, Table 3). Most cases of RMS occurred in the head and neck region (29.3%) and in the genito-urinary tract (26.3%) (Fig. 2A); alveolar subtypes ($n = 13$) occurred most commonly in the head and neck ($n = 8$). Metastatic stage was recorded in 20% of RMS (Fig. 2B) with recorded stage: in 9 of 53 embryonal, 5 of 12 alveolar and 1 of 16 NOS cases.

Fibrosarcoma was labelled in the SEER database under three ICD-O-3 codes: 8814/3, infantile fibrosarcoma ($n = 64$); 8810/3, fibrosarcoma-NOS ($n = 9$) and 8813/3, fascial fibrosarcoma ($n = 1$); in total, 74 cases were recorded. Fibrosarcoma showed predilection for limbs (44%) and trunk (30%), and metastatic disease was noted in only 8% of cases.

MRT were seen mainly in the kidneys, but were also reported at other sites; distant metastases were present in more than 50% of cases. Haemangiopericytoma ($n = 12$) was recorded to occur mainly in the head and neck region ($n = 9$), and no cases with distant stage were reported. For DFS ($n = 9$), the trunk was the most common location (7 out of 9 cases) and no metastatic cases were recorded at diagnosis. ESFT were seen more commonly in the extremities (4 out of 9 cases) and 3 patients had distant spread at diagnosis.

3.3. Outcome and prognostic factors of STS in infants

The outcome of infants with STS was significantly worse than for older children; with a median follow-up of 2.5 years (range, 0–33 years); the estimated 5-year OS rates for infants and older children were 62 ± 3.0% and 71 ± 0.9%, respectively ($P = 0.0002$, Fig. 3A).

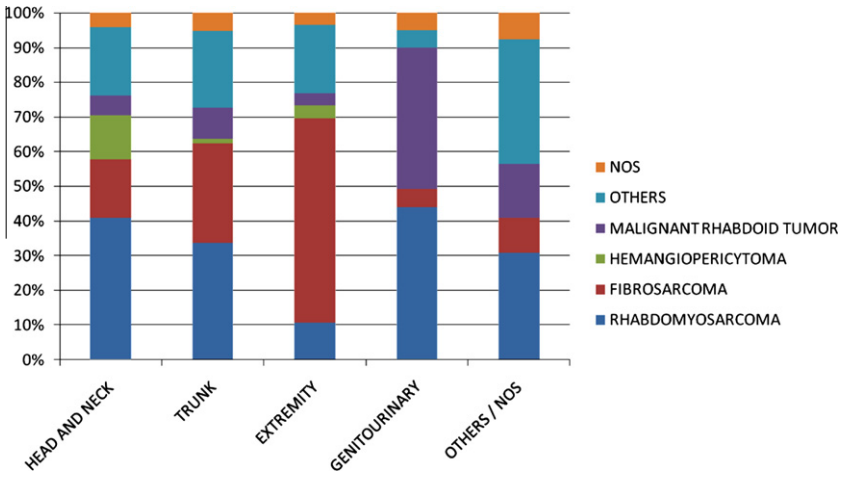

Fig. 1 – Bar histogram showing the distribution of different subtypes of soft tissue sarcomas in the first year of life according to the site of primary tumours.

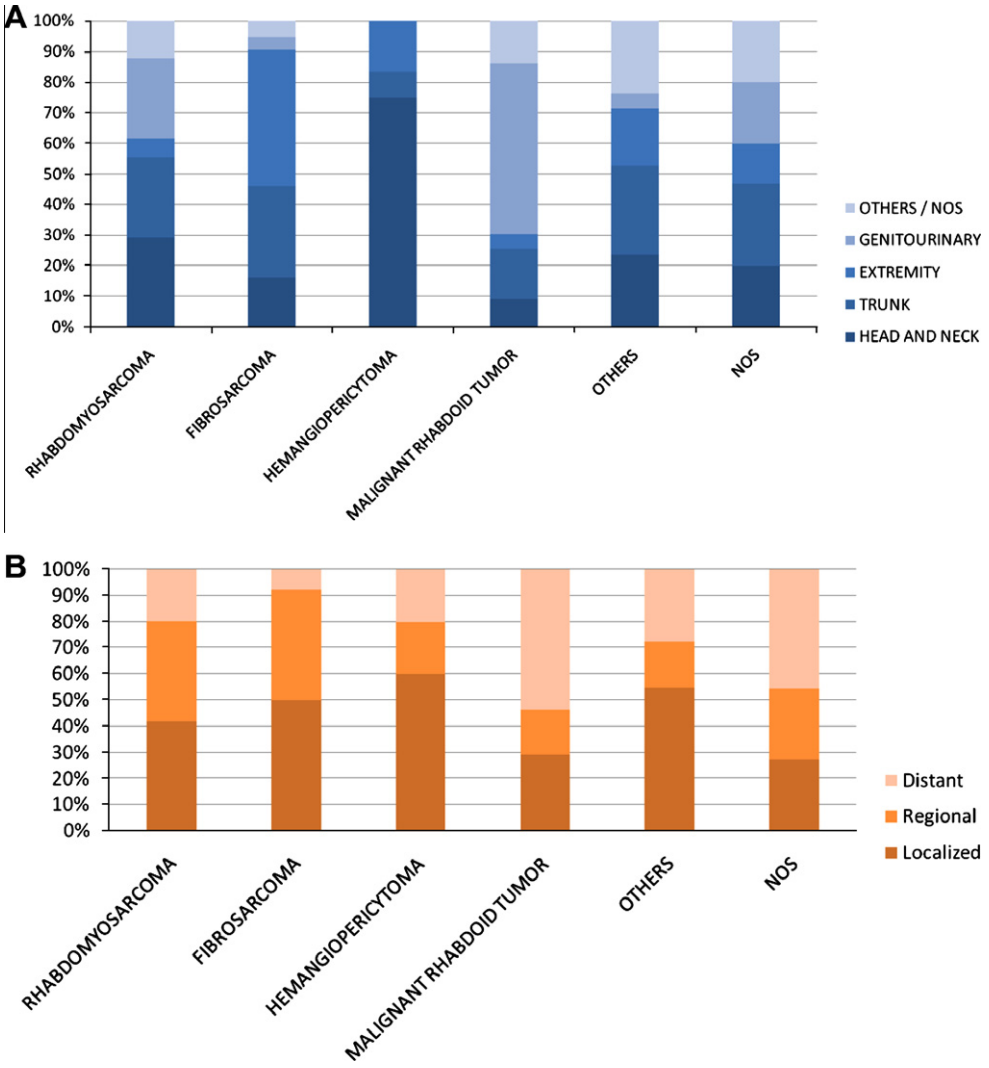

Fig. 2 – Bar histograms showing the different types of soft tissue sarcomas in the first year of life and the distribution of (A) primary tumour sites and (B) stage.

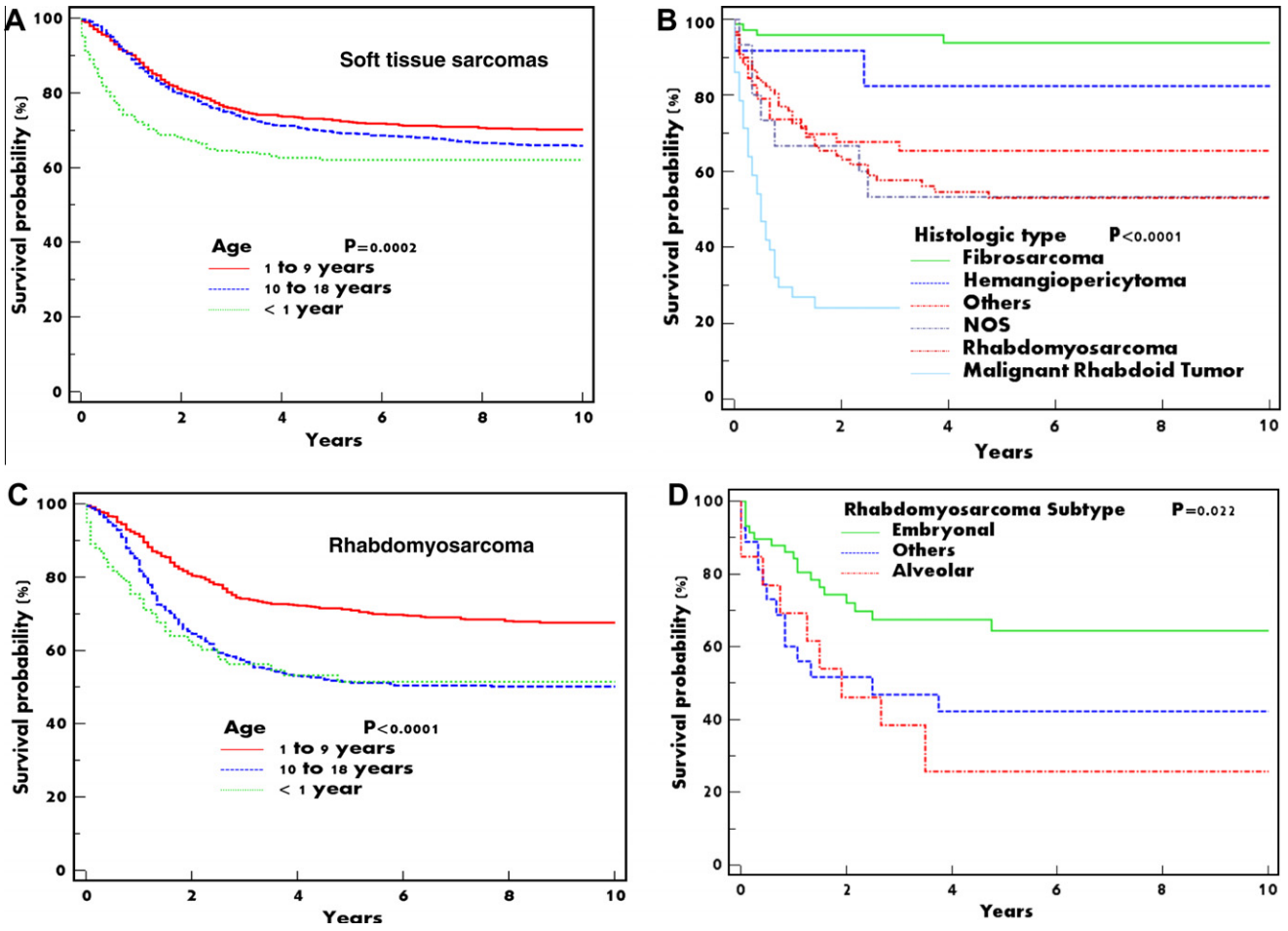

Fig. 3 – Kaplan–Meier curves showing the overall survival of (A) children with soft tissue sarcomas according to age at diagnosis, (B) infants less than one year with soft tissue sarcomas according to histologic subtype, (C) children with rhabdomyosarcoma according to age at diagnosis and (D) infants with rhabdomyosarcoma according to histologic subtype; curves were compared using the log-rank test with *P* values indicated on each panel.

There was great variability in survival according to histologic types, with infants with fibrosarcoma and haemangiopericytoma having the best outcome (5-year survival of 94 ± 3.1% and 83 ± 11%, respectively; Fig. 3B). Patients with MRT had the worst outcome (5-year OS, 24 ± 6.7%).

We then compared survival rates of infants and older children according to the various histotypes; infants had worse outcome in RMS (see below), but showed a tendency towards better survival in fibrosarcoma (5-year OS, 94 ± 3.1% versus 88 ± 2.8, $P = 0.15$; HR, 1.90; 95% CI, 0.79–4.55).

Different variables were then analysed in univariate models using the log-rank test. Gender and race were not found to be significant prognostic factors for survival ($P = 0.26$ and $P = 0.37$, respectively). As a group, extremity tumours were associated with better outcome than tumours at other sites ($P < 0.0001$). Tumour stage had a significant effect on survival; 5-year OS estimates were 77 ± 4.4% and 24 ± 5.9% for localised and metastatic disease, respectively ($P < 0.0001$).

When the three significant prognostic factors (site, stage and histology) were combined in a multivariate model using the Cox-proportional hazards regression model, primary tumour site lost significance (hazard ratio [HR], 1.71; 95% confidence intervals [CI], 0.79–3.75; $P = 0.18$), while histology "other than fibrosarcoma and haemangiopericytoma" (HR, 5.7; 95% CI, 2.28–14.20; $P = 0.00021$) and distant stage (HR, 5.15; 95% CI, 3.28–8.10; $P < 0.0001$) remained significantly associated with worse outcome.

No major details were available throughout the SEER database on treatment modalities; thus, it was not possible to explore the influence of therapy on survival. The only data recorded were the proportion of patients receiving surgery (with no details on surgical margins) and irradiation; infants were as likely as older children to undergo surgery (76% and 75%, respectively), but were significantly less likely to receive radiotherapy (18% versus 46%; $P < 0.0001$).

3.4. *Comparing RMS in infants and older children*

Because of the commonality of RMS in both age groups, we performed a separate analysis of this histologic subtype

(Table 4). Infants with RMS had a worse outcome than older children (5-year OS estimates 52 ± 5.5% versus 64 ± 1.4%, respectively; $P = 0.024$); interestingly, however, the survival of infants was similar to children 10–18 years old, but significantly worse than children 1–10 years old (Fig. 3C). Infants with the alveolar subtype had a significantly worse outcome than infants with embryonal RMS (5-year OS estimates 26 ± 14% versus 64 ± 7.0%, respectively; $P = 0.024$) (Fig. 3D).

The gender and race patterns were not statistically different when infants and older children were compared. Alveolar subtype was more frequent in older patients (26% versus 16% in infants). According to tumour site, there was a relatively high proportion of genito-urinary and trunk tumours in infants, while in older patients head and neck tumours as well as limb tumours were more frequent. In older patients, there was a higher frequency of distant stage (27% versus 16%). Surgical resection was performed in 72% of infants and 61% of older patients ($P = 0.044$), while radiotherapy was administered in 31% and 63%, respectively ($P < 0.0001$).

Table 4 – Patient characteristics, treatment modalities and outcome of infants and older children (1–18 years old) with rhabdomyosarcoma.

Variable	Less than 1 year old		1–18 years old		P
	N	(%)	N	(%)	
Sex					
Male	63	(63.6)	833	(58.8)	0.4
Female	36	(36.4)	583	(41.2)	
Race					
White	81	(81.8)	1116	(78.8)	0.11
Black	8	(8.1)	206	(14.5)	
Other	10	(10.1)	94	(6.6)	
Site					
Head and neck	29	(29.3)	531	(37.5)	0.02
Extremity	6	(6.1)	200	(14.1)	
Trunk	26	(26.3)	285	(20.1)	
Genitourinary	26	(26.3)	293	(20.7)	
Others/NOS	12	(12.1)	107	(7.6)	
Histologic subtype					
Embryonal	59	(59.6)	836	(59.0)	0.0007
Alveolar	13	(13.1)	365	(25.8)	
Others[a]	27	(27.3)	215	(15.2)	
Size					
<5 cm	32	(32.3)	475	(33.5)	0.84
⩾5 cm	24	(24.2)	324	(22.9)	
Not available	43	(43.4)	617	(43.6)	
SEER stage					
Localised/ regional	66	(66.7)	901	(63.6)	0.0036
Distant	16	(16.2)	389	(27.5)	
Unstaged	17	(17.2)	126	(8.9)	
Treatment modality					
Surgery done	71	(71.7)	864	(61.0)	0.044
Radiation given	31	(31.3)	896	(63.3)	<0.0001
5 year survival					
Embryonal histology	64 ± 7.0%		72 ± 1.7%		0.30
Alveolar histology	26 ± 14%		52 ± 3.0%		0.06
Other histologies[a]	42 ± 10%		54 ± 3.6%		0.069

Variables were compared using chi-square test (for categorical variables) and log-rank test (for survival).

[a] Including pleomorphic, mixed and not otherwise specified.

4. Discussion

In this population-based study we compared the clinical features and outcome of STS occurring in the first year of life with those of older children. Age was found to have a strong influence on the epidemiology of STS; there was a strong correlation between the incidence of the various STS histotypes, their natural history and outcome with age.

In absolute terms, STS under 1 year of age are rare tumours; it is known that most soft tissue tumours seen between birth and 12 months of age are generally benign.[12] However, the annual incidence recorded by the SEER database is 16.0 per million in the first year of life, higher than the incidence of STS in older children.

Our analysis confirms that the pattern of STS subtypes is different in patients under and over 1 year of age. RMS represents the largest individual diagnostic subgroup in both age groups, but in infants there is a higher proportion of fibrosarcoma, haemangiopericytoma and MRT. Most MRT primaries were located in the kidney; an analysis of the MRT cases collected in the SEER database has been recently reported.[3]

It has been reported that about 5–10% of all RMS cases occur in patients younger than 1 year old.[5,13–15] In the current series, 99 cases of infantile RMS were compared to 1461 cases occurring in older children. In infants, there was a relatively high proportion of genito-urinary and trunk primaries and a low proportion of alveolar subtype and metastatic cases. However, in spite of these two latter favourable findings, survival was significantly lower in infants when compared to children who were 1–10 years old.

Age less than 1 year emerged as an independent adverse prognostic factor in RMS.[15–17] In particular, in the Intergroup Rhabdomyosarcoma Study (IRS)-IV protocol[16,17] failure-free survival was 55% in infants, 83% in children aged 1–9 years and 68% in patients over 10 years. The possible reasons of this difference in outcome have not yet been clearly identified. This adverse outcome may be influenced by the subset of patients diagnosed in the neonatal period, who were recognised as having a particularly poor outcome.[5,9,18] Unfortunately, the SEER database does not permit the identification of congenital and neonatal cases.

While differences in biology may dictate this adverse outcome, we cannot underestimate the effect of the difficulties in delivering optimal therapy to infants with RMS; the particular vulnerability of young children to the acute and long-term effects of cancer therapy poses a great challenge to paediatric oncologists. Unacceptable toxicity was reported in the IRS I and II trials when full chemotherapy doses were used (5% of treatment-related deaths in infants versus 1% in older children),[13] suggesting that dose reduction is needed to

decrease life-threatening and fatal toxicities. Likewise, indications for radiotherapy have been usually limited in infants. This strategy has shown to result in a higher risk of local relapse; in particular, local failure was particularly high in patients whose disease stage would have warranted radiotherapy (i.e. incomplete resection, alveolar histotypes), but who were not irradiated due to their age.[15] An International Society of Pediatric Oncology-Malignant Mesenchymal Tumour (SIOP-MMT) study showed that the use of a conservative approach with limited radiotherapy for infants with RMS could result in a relatively high rate of local failure; however, the overall survival was comparable to other age groups, suggesting that those patients can be rescued with second-line treatments.[19]

The SEER database does not provide adequate details on treatment; our analysis, however, showed that radiotherapy was administered in around one third of infants and in two thirds of older children. While these data are very suggestive of a role for radiotherapy in the improved outcome of older children, it is not possible to define a causal association between the differences in radiotherapy administration and outcome in this series. The high percentage of infants with fibrosarcoma and haemangiopericytoma, which are not typically treated with radiation, can partially explain the reduced use of radiation in infants.

Lacking any evidence of biological differences between RMS arising before or after one year of age, a major challenge in the management of infants with RMS should be the improvement of treatment intensity and, more importantly, local control. A better use of alternative delivery methods such as brachytherapy, as well as the application of proton-beam radiation therapy, should be explored in this age group.

The second most frequent STS histotype in infants is fibrosarcoma. The SEER database does not distinguish between the infantile type and the adult-type fibrosarcoma, but these tumours have been clearly recognised as two biologically distinct entities. Infantile fibrosarcoma usually occurs under the age of 2 years, but its definition is not related to patient age, but to the identification of the specific t(12;15)(p13;q26) translocation and the ETV6-NTRK3 fusion transcript, which is shared with hypercellular mesoblastic nephroma.[20,21] Our analysis confirmed the excellent outcome of fibrosarcoma under 1 year of age and, by extrapolation, of infantile fibrosarcoma. The good response to chemotherapy and the excellent outcome of infantile fibrosarcoma[4] define an entity that is clearly distinct from adult-type fibrosarcoma.[22]

The small number of cases recorded for STS subtypes other than RMS and fibrosarcoma hinders further discussion on STS occurring in infants. One example is haemangiopericytoma which was associated with good outcome similar to what was described previously in the literature.[23,24] Despite the limitations of such a population-based analysis (i.e. lack of pathological review, inadequate data on administered treatment), this report attempts to shed a little more light on the epidemiology, clinical features and natural history of STS occurring in infants. The unique clinical and biologic characteristics of STS occurring in the very young suggest that age and histology appropriate treatment approaches should be developed.

Conflict of interest statement

None declared.

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