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HIGHLIGHTS

Incidence

- The soft tissue sarcomas of children and adolescents arise primarily from the connective tissues of the body, such as fibrous tissue, adipose tissue, and muscle tissue. The sarcomas that arise from bone are discussed separately in the bone tumor chapter.
- In the US, 850-900 children and adolescents younger than 20 years of age are diagnosed with soft tissue sarcomas each year, of which approximately 350 are rhabdomyosarcomas.
- The incidence of soft tissue sarcomas for children and adolescents younger than 20 years of age was 11.0 per million (Table IX.2), representing 7.4% of cancer cases for this age group.
- Rhabdomyosarcoma was the most common soft tissue sarcoma among children 0-14 years, representing nearly 50% of soft tissue sarcomas for this age range (Figure IX.1) with an incidence rate of 4.6 per million (Table IX.2).
- There are two major types of rhabdomyosarcoma: embryonal (about 75% of rhabdomyosarcoma cases) and alveolar. These two subtypes tended to occur at different body sites (Figure IX.3) and had different age patterns (Figure IX.2). The incidence of embryonal rhabdomyosarcoma was higher among children 0-4 years, while the incidence of alveolar rhabdomyosarcoma was similar throughout childhood (Figure IX.2).
- Other types of soft tissue sarcomas are rare and the incidence is higher in adolescents compared to younger children. Among these are the fibrosarcomas, malignant fibrous histiocytoma, synovial sarcoma, leiomyosarcoma, liposarcoma, and others (Table IX.2).
- For infants, the most common soft tissue sarcoma was embryonal rhabdomyosarcoma. However, a distinctive set of other soft tissue sarcomas can develop in infants (e.g., infantile fibrosarcoma and malignant hemangiopericytoma). These tumors are different from the types of soft tissue sarcomas that arise in adolescents (Table IX.2).
- Males had slightly higher incidence rates for soft tissue sarcomas than females for the period 1975-95 (Table IX.3).
- Black children had slightly higher incidence rates for soft tissue sarcomas than white children (Table IX.3), with the largest difference observed among 15-19 year olds.
- The incidence of soft tissue sarcomas among those younger than 20 years of age has not changed much between 1975-79 (10.2 per million) and 1990-95 (11.3 per million) (Table IX.4 and Figure IX.5).

Survival

- The overall 5-year survival rate for children with rhabdomyosarcoma was approximately 64% for cases diagnosed from 1985-94 (Figure IX.7). Younger children had higher survival rates than older children and adolescents, and children with embryonal rhabdomyosarcoma had a more favorable prognosis than children with alveolar rhabdomyosarcoma (Figure IX.7).

Risk factors

- Congenital anomalies and genetic conditions are the only known risk factors for soft tissue (Table IX.5).

INTRODUCTION

The soft tissue sarcomas of childhood are a heterogeneous group of malignancies primarily of mesenchymal cell origin that develop at primary sites throughout the body [1]. Mesenchymal cells normally mature into skeletal muscle, smooth muscle, fat, fibrous tissue, bone and cartilage. The malignant counterparts of normal soft tissue cells include: fibrosarcomas (fibrous tissue), liposarcomas (adipose tissue), leiomyosarcomas (smooth muscle), rhabdomyosarcomas (striated muscle), angiosarcomas and malignant hemangiopericytoma (blood vessels), synovial sarcomas (synovial tissue), and chondrosarcomas (cartilage) [1]. Tumors derived from peripheral nervous system tissues are also included within the soft tissue sarcoma category, including malignant peripheral nerve sheath tumors (also termed malignant schwannoma and neurofibrosarcoma),and extraosseous Ewing's sarcoma [1,2]. The sarcomas of bone are not included in this discussion, but are considered within the bone tumor chapter of this monograph.

In the US, 850-900 children and adolescents younger than 20 years of age are diagnosed with soft tissue sarcomas each year, of which approximately 350 are rhabdomyosarcomas. In children, soft tissue sarcomas generally are classified as either rhabdomyosarcomas (RMS) or non-rhabdomyosarcomas (non-RMS) [1,3,4], with the non-RMS being further divided into multiple histologic subtypes such as those listed in the preceding paragraph [5-8]. The International Classification of Childhood Cancer (ICCC) partitions soft tissue sarcomas into 5 subcategories [9]: a) the rhabdomyosarcoma subcategory (including embryonal and alveolar); b) the fibrosarcoma subcategory (fibromatous malignancies and malignant nerve sheath tumors); c) Kaposi's sarcoma; d) the "other specified" soft tissue sarcoma subcategory (including synovial malignancies; blood vessel malignancies; myomatous malignancies; lipomatous malignancies; and soft tissue (extraosseous) Ewing's sarcoma and peripheral neuroectodermal tumors) and, e) the "unspecified" soft tissue sarcoma subcategory. Individual characteristics of each subcategory are discussed in more detail in the sections that follow.

The various soft tissue sarcomas are associated with distinctive chromosomal alterations that can be used in some instances to support or confirm a specific diagnosis [10,11] (Table IX.1). Embryonal RMS tumor cells often show extra chromosome copies (hyperdiploidy) and loss of heterozygosity involving a specific site on the short arm of chromosome 11 [11]. Alveolar RMS tumors cells have translocations involving the FKHR gene on the long arm of chromosome 13 with genes of the PAX family on either chromosome 2 (PAX3) or chromosome 1 (PAX 7) [11]. Many of the non-RMS also show characteristic chromosome translocations. Of note, infantile fibrosarcoma tumor cells contain the same chromosomal abnormalities as the tumor cells of congenital mesoblastic nephroma, with both possessing t(12;15)(p13;q25)-associated ETV6-NTRK3 gene fusions [12]. Synovial sarcomas are virtually always associated with translocations that fuse the SYT gene on chromosome 18 with the SSX-1 or SSX-2 genes on the X chromosome [13-15]. Extraosseous Ewing's sarcoma and peripheral neuroectodermal tumors have translocations involving the EWS gene on chromosome 22 and either the FLI1 gene on chromosome 11 or the ERG gene on chromosome 21 [16]. Malignant peripheral nerve sheath tumors (also known as neurofibrosarcomas, malignant schwannomas, and neurogenic sarcomas) are associated with neurofibromatosis 1 (NF1) [17], the gene for which is located on the long arm of chromosome 17 [18]. The occurrence of characteristic chromosomal translocations among many of the soft

Table IX.1: Molecular characterization of soft tissue sarcomas

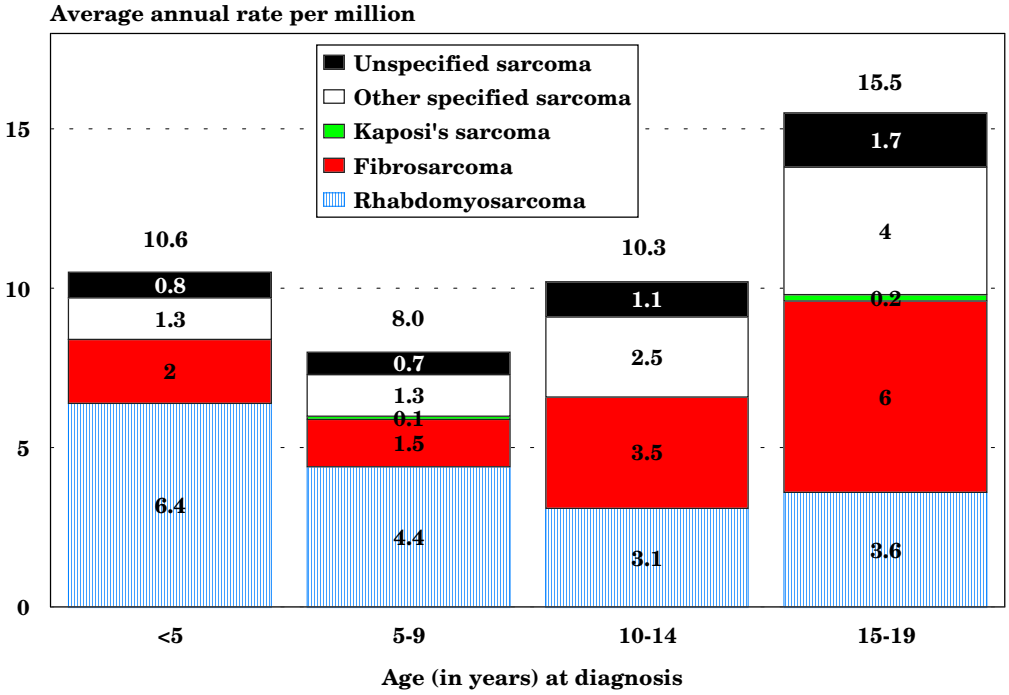
Diagnosis	Chromosomal Abnormality	Genes Involved
Rhabdomyosarcoma, Embryonal [11]	Hyperdiploidy, and loss-of-heterozygosity at chromosome 11p15	Unidentified gene at chromosome band 11p15
Rhabdomyosarcoma, Alveolar [11]	t(2;13) or t(1;13)	FKHR on chromosome 13 and PAX 3 (chromosome 2) or PAX7 (chromosome 1)
Infantile fibrosarcoma [22,23]	t(12;15)	TEL (ETV6) gene on chromosome 12 and NTRK3 (TRKC) on chromosome 15.
Dermatofibrosarcoma protuberans [24,25]	t(17;22)	Platelet-derived growth factor b-chain (PDGFB) gene on chromosome 17 and collagen type I alpha 1 (COL1A1) on chromosome 22
Malignant peripheral nerve sheath tumors (also known as neurofibrosarcomas and malignant schwannomas) [26,27]	Abnormalities of Chromosome 17	Neurofibromatosis 1 (NF1) gene
Synovial sarcoma [13-15]	t(X;18)	SYT on chromosome 18 and SSX-1 or SSX-2 on the X chromosome
Liposarcoma [28-30]	t(12;16),	FUS gene on chromosome 16 and CHOP gene on chromosome 12
Chondrosarcoma, Myxoid [31,32]	t(9;22)	EWS gene on chromosome 22 (also associated with Ewing's sarcoma) and TEC gene on chromosome 9
Extra-osseuous Ewing's sarcoma and peripheral neuroectodermal tumor (PNET) [33]	t(11;22)	EWS gene on chromosome 22 and FLI gene on chromosome 11.
Alveolar soft part sarcoma [34,35]	t(X; 17)	Unidentified gene at chromosome band 17q25

tissue sarcomas of children and adolescents is in contrast to the rarity of such translocations among the epithelial solid tumors that predominate among adults, with the reason(s) for this difference not understood.

INCIDENCE

From 1975-95 in SEER areas, 2,182 neoplasms in children younger than 20 years of age were classified into the ICCC soft tissue sarcoma diagnostic category. The ICCC soft tissue sarcoma category is primarily based on histology and not anatomic site. Thus, nearly one-half of the cases (974) occurred at anatomic sites other than connective tissue, with RMS showing a particular propensity for arising at anatomic sites throughout the body (see RMS discussion below). Conversely, there were 512 cancers among children arising in anatomic sites coded as connective tissues

Figure IX.1: Soft tissue sarcoma age-specific incidence rates by ICCC subcategory, all races, both sexes, SEER, 1975-95



that were not included in the ICCC soft tissue sarcoma category (including 373 classified in the ICCC sympathetic nervous system tumor category and 77 classified in the ICCC category germ cell, trophoblastic, and other gonadal tumor category). These cases have been included in the appropriate chapters in the monograph.

Average annual incidence rates of soft tissue sarcomas are shown in Table IX.2. Overall, the age-adjusted rate of soft tissue sarcomas was 11.0 per million children younger than 20 years of age, which represented 7% of all primary malignancies for this population. Of these, 40% were RMS, 29% were in the ICCC fibrosarcoma subcategory, 21% were in the "other specified" soft tissue sarcoma subcategory, and 10% were unspecified soft tissue sarcomas. Kaposi's sarcoma, a disease associated with AIDS, was extremely rare in this population, with only 18 cases reported to SEER areas during 1975-95.

Histology-specific incidence

Table IX.2 provides the incidence of specific diagnoses within each of the ICCC soft tissue sarcoma subcategories. The incidence of soft tissue sarcoma subtypes differed notably by age as illustrated in Figure IX.1. RMS represented 60% of soft tissue sarcomas for children younger than 5 years of age, but the relative frequency of RMS decreased with each successive 5-year age group; RMS accounted for only 23% of soft tissue sarcomas among the 15-19 year-old group. The opposite pattern occurred for the non-RMS subcategories, which represented 40% of soft tissue sarcomas among children younger than 5 years of age, but 77% of these tumors among 15-19 year-olds. The primary diagnoses for each subcategory are listed and briefly described below.

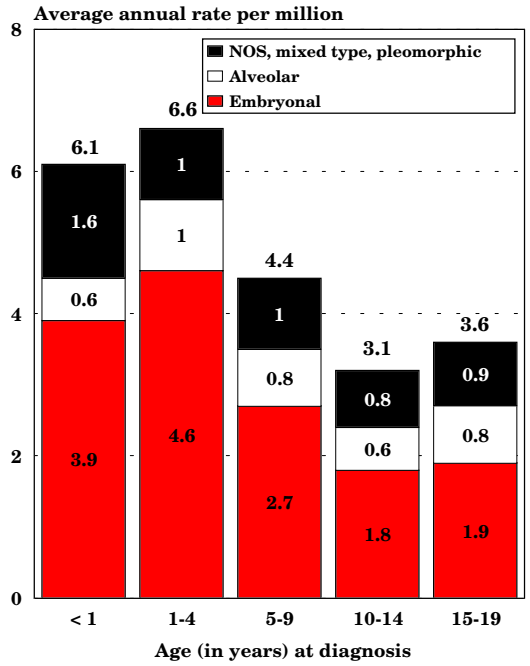
The RMS subcategory (ICCC IXa) is comprised of embryonal and alveolar RMS,

Table IX.2: Age-specific and age-adjusted incidence rates per million of soft tissue sarcomas by ICCC group and subcategory, all races, both sexes, SEER 1975-95

		Age (in years) at diagnosis					
	ICD-O-2 Codes	<5	5-9	10-14	15-19	Total* <15	Total* <20
Soft Tissue Sarcomas (IX)		**10.6**	**8.0**	**10.3**	**15.5**	**9.6**	**11.0**
Rhabdomyosarcoma Subcategory (IXa)		**6.4**	**4.4**	**3.1**	**3.6**	**4.6**	**4.3**
Embryonal rhabdomyosarcoma	8910	4.4	2.7	1.6	1.8	3.0	2.6
Alveolar rhabdomyosarcoma	8920	0.8	0.8	0.6	0.8	0.7	0.7
Rhabdomyosarcoma, NOS, pleomorphic, etc.	8900-8902, 8991	1.2	0.9	0.9	0.9	1.0	1.0
Fibrosarcoma Subcategory (IXb)		**2.0**	**1.5**	**3.5**	**6.0**	**2.3**	**3.2**
Fibrosarcoma	8810	0.3	0.3	0.5	1.1	0.4	0.6
Infantile fibrosarcoma	8814	0.7	0.0	0.0	0.0	0.2	0.2
Malignant fibrous histiocytoma	8830	0.4	0.4	0.7	1.7	0.5	0.8
Dermatofibrosarcoma	8832	0.2	0.5	1.2	1.9	0.7	1.0
Malignant peripheral nerve sheath tumor	9540,9560	0.2	0.2	0.8	1.2	0.4	0.6
Kaposi's sarcoma (IXc)	9140	**0**	**0.1**	**0**	**0.2**	**0**	**0.1**
Other specified STS Subcategory (IXd)		**1.3**	**1.3**	**2.5**	**4.0**	**1.8**	**2.3**
Liposarcoma	8850,8852,8854	0.1	0.0	0.1	0.4	0.1	0.1
Leiomyosarcoma	8890, 8891	0.1	0.2	0.2	0.7	0.2	0.3
Malignant mesenchymoma	8990	0.3	0.2	0.1	0.1	0.2	0.2
Synovial sarcoma	9040, 9041 9043	0.1	0.3	0.8	1.4	0.4	0.7
Hemangiosarcoma & Malignant Hemangioendothelioma	9120, 9130, 9133	0.1	0.1	0.1	0.3	0.1	0.2
Hemangiopericytoma, malignant	9150	0.2	0.1	0.1	0.1	0.1	0.1
Alveolar soft part sarcoma	9581	0.1	0.1	0.1	0.1	0.1	0.1
Chondrosarcoma	9231, 9240	0.0	0.0	0.2	0.0	0.1	0.1
Ewing's (extraosseous) Family	9364, 9260	0.2	0.3	0.4	0.6	0.3	0.4
Unspecified Subcategory (IXe)	8800-8804	**0.8**	**0.7**	**1.1**	**1.7**	**0.9**	**1.1**

* Adjusted to the 1970 US standard population

Figure IX.2: Rhabdomyosarcoma (RMS) age-specific incidence rates by subtype and age group all races, both sexes, SEER, 1976-84 and 1986-94 combined

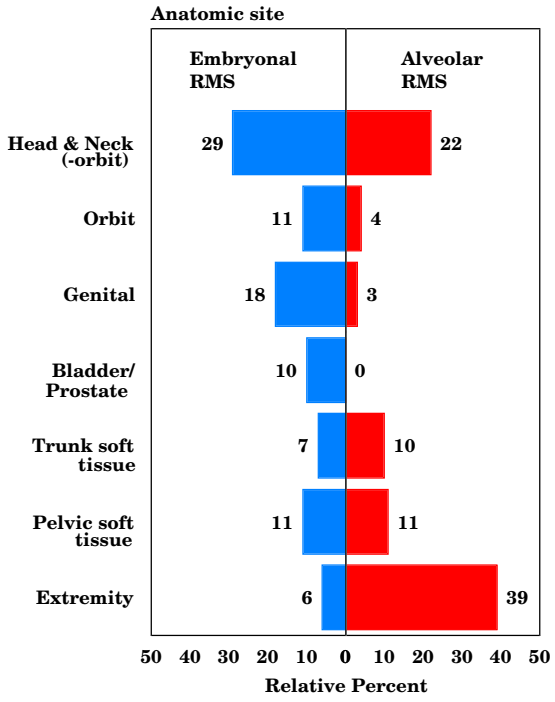


as well as "not otherwise specified" RMS, pleomorphic RMS, mixed-type RMS, and embryonal sarcoma. RMS 'not otherwise specified' (NOS) represented 17% of all RMS in SEER areas for 1975-95. Embryonal RMS was the most common type of RMS at all ages and accounted for 75% of cases for those younger than 20 years of age with a specific RMS diagnosis (i.e., excluding the NOS category). However, as shown in Figure IX.2, the incidence of embryonal RMS varied by age. The relative percentage of RMS decreased with increasing age, from 83% of cases with a specific RMS diagnosis among children younger than 5 years of age to 64% of cases among 15-19 year olds. The relative percentage of alveolar RMS showed a corresponding increase, from 15% of cases with a specific RMS diagnosis among children younger than 5 years of age to 30% of cases among 15-19 year olds. Pleomorphic (1.5%) and mixed type RMS (1.0%) comprised only a small percentage of total RMS.

Embryonal RMS occurred at sites throughout the body (Figure IX.3), with the head and neck region (excluding the orbit) being most common (29% of cases). RMS arising in the orbit, which is known to have an especially favorable prognosis [19], represented an additional 11% of embryonal RMS cases. Genital and urinary organ sites were also common locations of RMS development (18% and 10% of embryonal RMS cases, respectively), while the extremities were an uncommon site for embryonal RMS (only 6% of embryonal RMS cases). By comparison, alveolar RMS occurred most commonly at extremity sites (39% of alveolar RMS cases) and occurred infrequently at genitourinary sites (3% of cases).

The fibrosarcoma subcategory (ICCC IXb) includes the following diagnoses (incidence rates for the younger than 20 year old population are provided in parentheses): dermatofibrosarcoma (1.0 per million), malignant fibrous histiocytoma (0.8 per million), fibrosarcoma (0.6 per

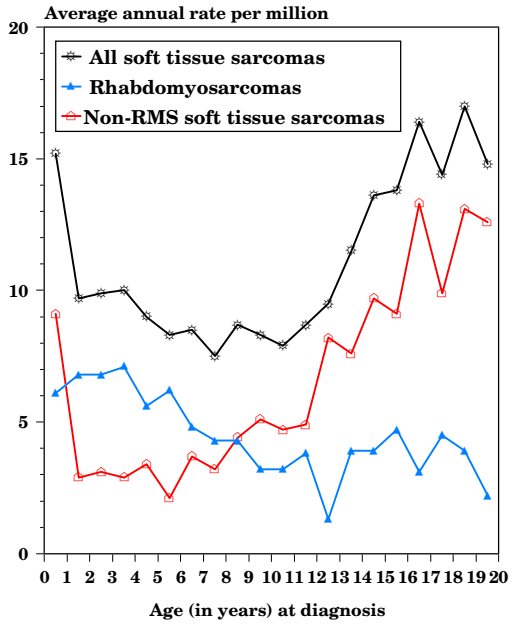
Figure IX.3: Percent distribution of embryonal and alveolar rhabdomyosarcoma (RMS) by anatomic site age <20, all races, both sexes, SEER, 1975-95



million), malignant peripheral nerve sheath tumor (0.6 per million), and infantile fibrosarcoma (0.2 per million). Each of these soft tissue sarcomas, save infantile fibrosarcoma, occurs in adults as well as in children [7,20]. With the exception of infantile fibrosarcoma, each of these diagnoses occurred at higher incidence among the 15-19 year old population than among any of the younger age groups (Table IX.2). Infantile fibrosarcomas, which are known for their excellent outcome with surgery alone [7], occurred only in the younger than 5-year age group.

For the "other specified" soft tissue sarcoma subcategory (ICCC IXd), synovial sarcoma was the most common subtype (0.7 per million), followed by the Ewing's (extraosseous) family of tumors (0.4 per million) and leiomyosarcoma (0.3 per million) (Table IX.2). Blood vessel tumors (e.g., hemangiosarcomas and malignant hemangiopericytoma), liposarcomas, and alveolar soft part sarcomas occurred less commonly. As with the ICCC fibrosarcoma subcategory, most diagnoses occurred at higher rates among the 15-19 year old group than among younger age groups. Exceptions were malignant mesenchymoma and malignant hemangiopericytoma, which developed most frequently in the first five years of life.

Figure IX.4: Soft tissue sarcoma age-specific incidence rates by histology, all races, both sexes SEER, 1976-84 and 1986-94 combined



Age-specific incidence

Figure IX.4 shows incidence rates for soft tissue sarcomas by single year of age[1]. Incidence rates were highest among young children during infancy. Rates dropped in the second year of life, and remained fairly stable through age 10 years. After age 10 years, incidence rates began to rise again as a result of increasing rates for the non-RMS soft tissue sarcomas. Among infants, the overall incidence was 15.2 per million, compared to approximately 10 per million for children ages 1-4 years. Non-RMS tumors strongly contributed to the peak in soft tissue sarcoma incidence during infancy. While RMS accounted for approximately 40% of soft tissue sarcomas among infants, RMS occurred at a similar rate among children 1-4 years. The non-RMS diagnoses that occurred more commonly in the first year of life than in the succeeding 4 years included: infantile fibrosarcoma and fibrosarcoma, NOS (22% of infant soft tissue sarcomas); malignant hemangiopericytoma (5% of infant soft tissue sarcomas), and malignant mesenchymoma (5% of infant soft tissue sarcomas).

[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84 and the 1990 estimates were used for cases diagnosed from 1986-94.

Table IX.3: Age-specific and age-adjusted incidence rates per million of soft tissue sarcomas, by race and sex, SEER, 1975-95

	Age (in years) at Diagnosis					
ICCC Group	**<5**	**5-9**	**10-14**	**15-19**	**<15***	**<20***
All races/Both sexes	10.6	8.0	10.3	15.5	9.6	11.0
Whites	10.5	7.8	9.9	14.2	9.4	10.6
Blacks	9.6	9.0	11.8	18.9	10.2	12.4
Males	11.2	9.0	10.7	16.2	10.3	11.8
Females	9.9	6.9	9.8	14.7	8.8	10.3

* Adjusted to the 1970 US standard population

Sex-specific incidence

Incidence rates for males and females are also shown in Table IX.3. Rates among males tended to be higher than rates for females within all age groups, although the overall difference was slight (11.8 per million males versus 10.3 per million females for the younger than 20 year old population). The pattern of rates by age and histologic subgroups were essentially the same for males and females.

Black-white differences in incidence

Table IX.3 shows incidence rates by 5-year age groups for both white and black children. Black children had slightly higher incidence rates overall than white children. Although rate differences were slight within all age groups, the largest difference occurred among those 15-19 years of age. To the extent that numbers allowed reliable comparisons, there were no notable racial differences in soft tissue sarcoma rates by histologic subgroups.

TRENDS

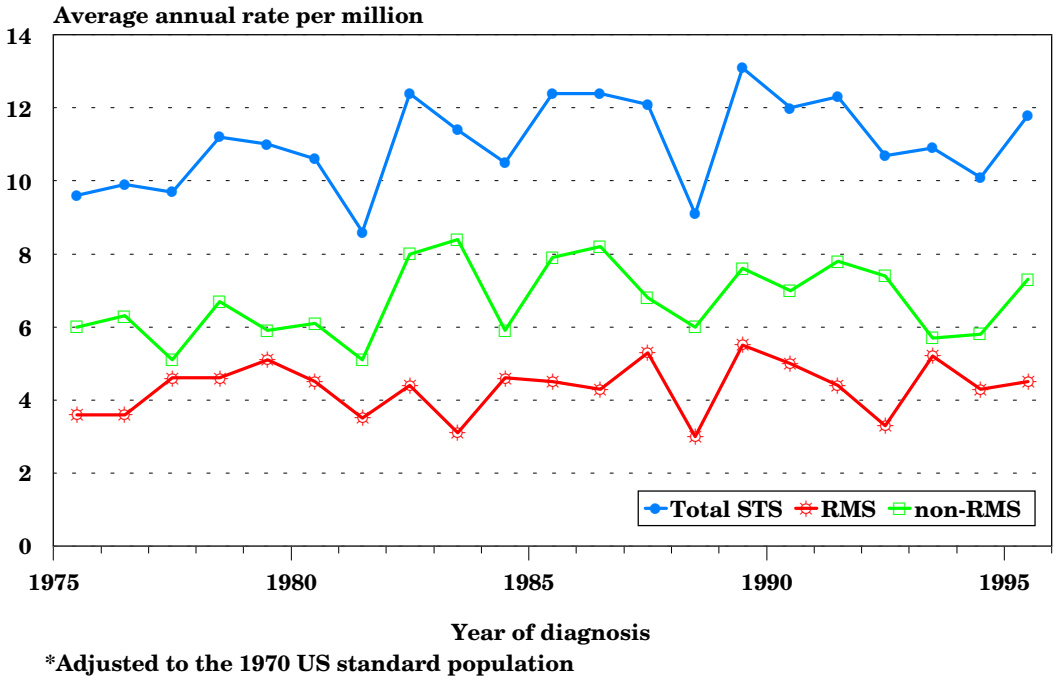
Average annual age-adjusted incidence rates across 5-year time periods (6 years for the last period) are shown in Table IX.4. Overall rates for soft tissue sarcomas increased slightly over the first three time periods from 10.2 to 11.8 per million, and then dropped a small amount in the 1990-95 period to 11.3 per million. Figure IX.5 shows the incidence rates for individual years from 1975-95 for total soft tissue sarcomas, RMS, and non-RMS soft tissue sarcomas. This figure illustrates the small changes in incidence during this period; RMS incidence was fairly stable at 4 per million and non-RMS soft tissue sarcoma incidence varied between 6 and 8 per million.

Table IX.4: Age-adjusted* incidence rates per million of soft tissue sarcomas by time period, race, and sex, age <20, SEER, 1975-95

	1975-79	**1980-84**	**1985-89**	**1990-95**
All races/Both sexes	10.2	10.7	11.8	11.3
Whites	10.1	10.4	11.5	10.4
Blacks	10.2	10.5	14.5	13.9
Males	11.0	10.6	13.1	12.2
Females	9.5	10.7	10.5	10.3

*Adjusted to the 1970 US standard population

Figure IX.5: Trends in total soft tissue sarcoma, rhabdomyosarcoma(RMS) and non-RMS age-adjusted* incidence rates, age <20, all races, both sexes SEER 1975-95



*Adjusted to the 1970 US standard population

SURVIVAL

Figure IX.6 shows survival rates for the time periods 1975-84 and 1985-94. The 5-year relative survival rate for all soft tissue sarcomas combined was 71% from 1985-1994, with little change from the earlier period of 1975-84. Survival rates were higher for the non-RMS fibrosarcoma subcategory and the "other specified" soft tissue sarcoma subcategory than for rhabdomyosarcoma. A small survival improvement in RMS occurred from the earlier to the later period (59% to 64% 5-year survival), but no difference between the two time periods was observed for either the fibrosarcoma subcategory (82% 5-year survival) or for the "other specified" soft tissue sarcoma subcategory (74% 5-year survival).

Figure IX.6: Soft tissue sarcoma 5-year relative survival rates, age <20, all races both sexes, SEER, 1975-84 and 1985-94

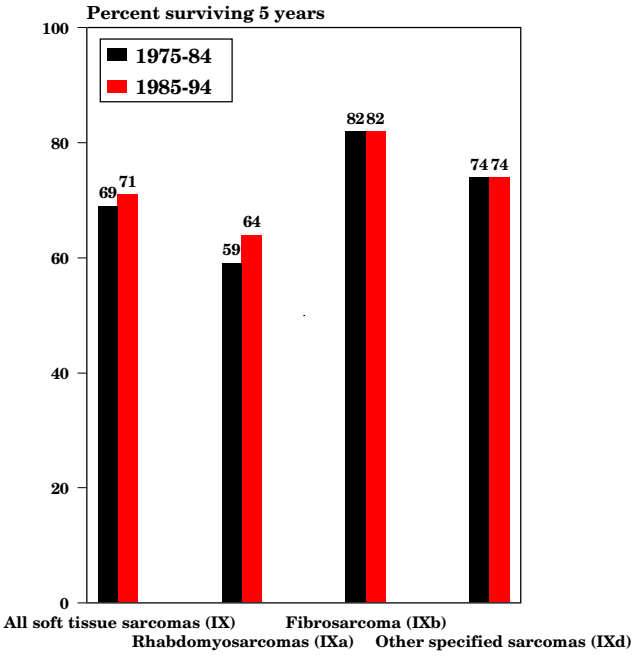
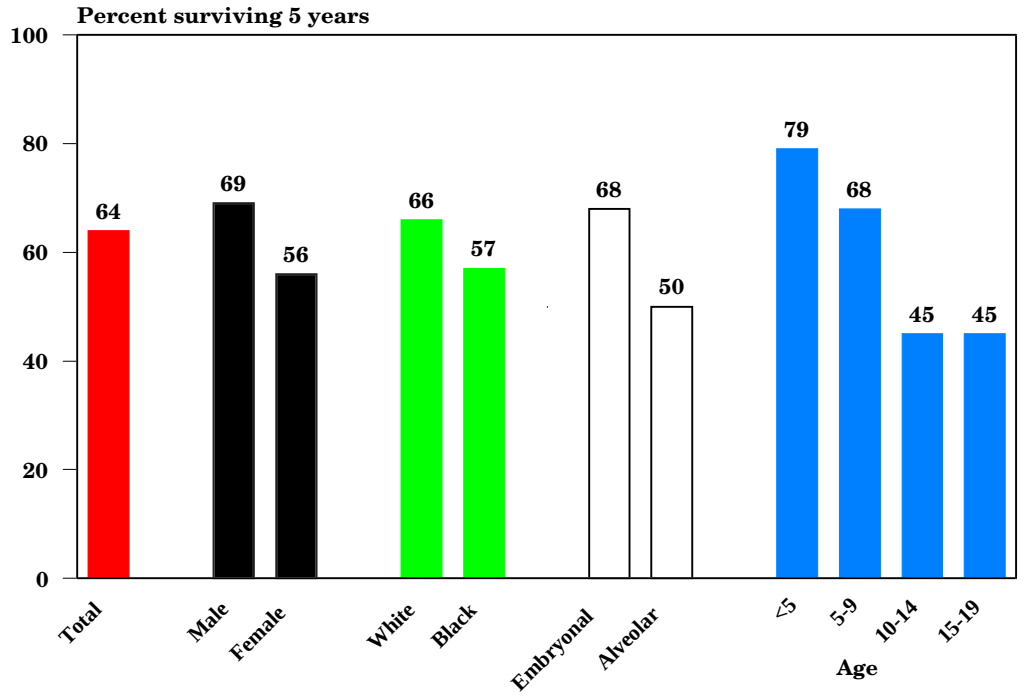


Figure IX.7: Rhabdomyosarcoma 5-year relative survival rates by sex, race, subtype, and age, SEER 1985-94



Additional data on 5-year relative survival of RMS are shown in Figure IX.7. Survival among males with RMS was better than that of females, and survival was somewhat higher for white children than for black children. Figure IX.7 also demonstrates the important prognostic advantage of younger age. Children younger than 5 years of age had much higher 5-year survival rates than 15-19 year olds (79% versus 45%). The prognostic advantage associated with younger age may be partially explained by the higher percentage of embryonal cases among young children, since RMS cases with embryonal histology are associated with superior outcome compared to cases with alveolar histology (Figure IX.7).

RISK FACTORS

Very little population-based research has been conducted on potential causes of RMS or other soft tissue sarcomas in children. Table IX.5 provides a brief summary of risk factors that have been explored. Certain congenital anomalies and genetic conditions are the strongest known risk factors, although they explain only a small proportion of cases. While the overwhelming majority of RMS occurs sporadically, a small proportion of RMS is associated with Li-Fraumeni cancer susceptibility syndrome (21), and probably neurofibromatosis type I (3).

SUMMARY

Soft tissue sarcomas accounted for 7% of all primary malignancies in SEER areas for children younger than 20 years of age from 1975-95. RMS represented approximately 40% of soft tissue sarcomas, with the remaining non-RMS cases being spread among multiple diagnoses primarily within the ICCC fibrosarcoma subcategory and the "other specific" soft tissue sarcomas subcategory. The average age-adjusted incidence

Table IX.5: Risk factors for soft tissue sarcomas in children

Exposure or Characteristic	Comments	References
Known risk factors		
Congenital anomalies	There is some concordance with the anatomic location of RMS and major birth defects. One autopsy study showed 32% of 115 children and adolescents with RMS to have at least one congenital anomaly.	36,37
Genetic conditions	Li-Fraumeni syndrome (associated with p53 mutations), and neurofibromatosis (associated with NF1 mutations)	21,38,39
Factors for which evidence is inconsistent or limited		
Socioeconomic status	Low socioeconomic status is associated with increased risk.	40
Ionizing radiation (in utero)	Diagnostic x-rays during pregnancy were associated with 2-fold increase in risk in one study.	41
Parental use of recreational drugs	Parents use of marijuana and cocaine during the pregnancy was associated with increased risk in one study.	37,42

rate of all soft tissue sarcomas combined was 11 per million children younger than 20 years of age. While RMS was the most common soft tissue sarcoma in children, especially in young children, in older adolescents the non-RMS tumors were more common than RMS, although no single non-RMS diagnosis accounted for more than 15% of all cases. There have been very few population-based studies to evaluate risk factors for soft tissue sarcoma occurrence; factors have been identified that explain only a very small proportion of cases. Five-year survival rates of soft tissue sarcomas improved only slightly from the period 1975-84 (69%) to 1985-94 (71%). Children with RMS had a somewhat poorer 5-year survival (64%) than did children with non-RMS in the fibrosarcoma subcategory (82%) and the "other specified" soft tissue sarcoma subcategory (74%). Males tended to have slightly better survival rates than females, and white children tended to fare better than black children. Younger children with RMS had better outcome than did older children (Figure IX.7).

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