

Sarcomas in Children, Adolescents and Young Adults

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Overview/Epidemiology

Soft tissue sarcomas (STS) are a heterogeneous and challenging group of cancers to treat in pediatric oncology. They can be broadly divided into rhabdomyosarcomas (RMS) and non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). Together, STS make up about 1% of all cancers in the general population but are more common in children, representing 7% of cancers in patients under 20 years old. Rhabdomyosarcomas make up nearly half of all STS in children, and the annual incidence is approximately 4.3 per million individuals under 20 years, or about 350 new cases per year in the United States.

There is a difference in age predilection with 2/3 of RMS cases occurring in children under 6 years, whereas cases of NRSTS account for 75% of STS in children ages 15 to 19. While the vast majority of STS cases are sporadic, there is a slight association with RMS and familial cancer syndromes, most notably Neurofibromatosis type 1 (NF1), Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome. For NRSTS, the associations are sometimes more pronounced. For example, malignant peripheral nerve sheath tumors (MPNST) occur in 7-13% of patients with NF1, and up to 28% of patients with familial adenomatous polyposis develop desmoid tumors.

5-YEAR OVERALL SURVIVAL		
DISEASE PROCESS	AKRON CHILDREN'S HOSPITAL	SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS PROGRAM (SEER)
ALVEOLAR RHABDOMYOSARCOMA	50%	64%*
EMBRYONAL RHABDOMYOSARCOMA	67%	64%*
NON-RHABDOMYOSARCOMA SOFT TISSUE SARCOMAS	40%	38.4%**

*Rhabdomyosarcoma **SEER Non-Rhabdomyosarcoma cases were classified as high-risk

Molecular Biology/Genetics

Rhabdomyosarcoma can be classified into 2 major histologic subgroups called alveolar and embryonal rhabdomyosarcoma. Each type has characteristic genetic alterations that are presumed to play a role in their pathogenesis. Alveolar rhabdomyosarcoma is distinguished by a genetic translocation resulting in a fusion transcription factor PAX-FOXO1 A that contributes to the development of the cancer phenotype. Embryonal rhabdomyosarcoma is thought to arise at least in part from a genetic alteration known as imprinting, whereby only the paternal genetic material is expressed at particular allele, in this case the IGF-2 gene, which codes for a growth factor involved in the pathogenesis of RMS.

The 3 most common histologic subtypes of NRSTS are MPNST, synovial sarcoma and undifferentiated soft tissue sarcoma. NRSTS comprise approximately 50% of all STS and have considerable variability in biology, prognosis and treatment. However, like rhabdomyosarcoma, many NRSTS tumors have characteristic cytogenetic abnormalities that are not only important in establishing prognosis. For example, 90% of synovial sarcomas contain a translocation involving the SSX1 or SSX2 gene on the X chromosome, with SSX1-containing tumors having higher rates of proliferation and metastatic disease, as well as shortened survival compared to SSX2 tumors.

Prognosis/Treatment

Patients with pediatric STS require the care of a specialized, multidisciplinary team with experience treating these tumors, including pediatric oncology, pediatric surgery and radiation oncology. The outcomes for many patients with RMS are good, however certain subgroups, including those with alveolar histology or with metastatic disease, have much lower rates of long-term cure. Disease stage and risk stratification are ultimate prognostic indicators for RMS. They were developed over time by successive clinical trials performed by the Intergroup Rhabdomyosarcoma Study Group, a clinical cooperative.



CASES

ALVEOLAR RHABDOMYOSARCOMA	4
EMBRYONAL/SPINDLE CELL RHABDOMYOSARCOMA	12
OTHER RHABDOMYOSARCOMA	2
NON-RHABDOMYOSARCOMA SOFT TISSUE SARCOMAS (PRIMARILY CLASSIFIED AS HIGH-RISK)	15
TOTAL	33

Clinical staging takes into account location, size and invasiveness of the primary tumor, lymph node involvement and the presence of metastatic disease. Treatments are assigned based on their risk for failure, which hinges on both the disease stage at diagnosis and the extent of remaining disease following surgical resection of the primary tumor. Various factors are associated with good outcomes, including small tumor size, non-parameningeal head and neck primary sites, complete surgical resection and embryonal histology. The standard chemotherapy regimen for RMS has been vincristine, dactinomycin and cyclophosphamide. Prognostic factors for NRSTS include patient age, tumor size and extent of primary resection, as well as tumor histologic subtype and grade. Due to the generally poor response rate of NRSTS to systemic chemotherapy as a whole, complete surgical resection remains the key mode of therapy for these cancers. When chemotherapy is pursued for cases of incomplete resection or metastatic disease, most regimens use a doxorubicin and ifosfamide backbone.

Future Direction: Targeted Therapy

As our knowledge increases regarding the specific molecular pathways involved in the development of cancer, we have applied these insights into the development of new treatment strategies. Targeting these pathways with newer classes of medications including mTOR inhibitors and tyrosine kinase inhibitors has generated new promise for improved outcomes for all types of cancer, including RMS and NRSTS. Akron Children's continues to be at the forefront of this technology with its recently developed Shannon E. Wilkes Targeted Therapy Program. Through this program, we can identify specific pathways in individual cancers, so they may be targeted for treatment with new therapies. We can also bank these tumors for future research.