Multidisciplinary Management of Pediatric Soft-Tissue Sarcoma

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The management of pediatric soft-tissue sarcomas has improved drastically through the use of multimodal therapy. These tumors include rhabdomyosarcomas and nonrhabdomyosarcomas. Both are staged using

The informative article by Neville et al discusses some of the issues that are most pertinent to the management of pediatric soft-tissue sarcoma. Over the past 3 decades, multi-institutional trials in the United States and Europe have shed significant light on the optimal management of rhabdomyosarcoma. However, therapeutic guidelines have been lacking for the group of sarcomas collectively termed nonrhabdomyosarcomatous soft-tissue sarcomas. These two subsets of soft-tissue sarcomas have important fundamental differences that underlie the radically different diagnostic and therapeutic approaches used for their management.

Effect of Age on Therapy
Rhabdomyosarcoma commonly affects children during the first decade of life. In the Intergroup Rhabdomyosarcoma Study (IRS) III,[1] 66% of patients were aged 10 years or less (median: 5 years) at the time of their diagnosis.
In contrast, the median age of children with newly diagnosed nonrhabdomyosarcomatous soft-tissue sarcomas was 12.3 and 11.2 years in two series. Moreover, according to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, 77% of soft-tissue sarcomas among patients in the 15- to 19-year-old age group were classified as nonrhabdomyosarcomatous soft-tissue sarcomas.[2-4]
These differences significantly affect the selection of local control therapies, because younger patients are at a greater risk of developing long-term complications from certain therapies, especially radiation therapy.

Primary Tumor Site and Clinical Group
Rhabdomyosarcoma most commonly affects the head and neck region. Of the more than 2,700 patients enrolled in three consecutive IRS trials, 35% had head and neck tumors. The next most common site was the genitourinary tract (24%).[5] Nonrhabdomyosarcomatous soft-tissue sarcomas, in contrast, more often arise in the extremities or the trunk.[3,4,6] Their potential resectability in the extremities may explain the preponderance of clinical groups I and II nonrhabdomyosarcomatous soft-tissue sarcomas and group III rhabdomyosarcoma in most series.

Histology and Molecular Biology
Rhabdomyosarcoma comprises two main histologic subtypes: embryonal and alveolar. The embryonal variant has no tumor-specific translocations, but does show inactivation of a putative tumor-suppressor gene. Alveolar rhabdomyosarcoma and several of the nonrhabdomyosarcomatous soft-tissue sarcomas have tumor-specific translocations. Fusion transcripts created by these translocations are presumed to be potent transcriptional activators that may regulate downstream genes and promote tumor formation or progression (Table 1).
Our center now uses sensitive techniques, such as reverse-transcriptase polymerase chain reaction, to detect these transcripts in a variety of soft-tissue sarcomas. In this way, we can corroborate diagnosis and detect minimal residual disease. The subtype of fusion transcript has proven to have prognostic significance in several soft-tissue sarcomas[7-10] and may become an integral part of the staging and risk assignment of these tumors.

Sites of Dissemination
Because nonrhabdomyosarcomatous soft-tissue sarcomas typically metastasize to the lung, a computed tomography scan of the chest is included in the initial diagnostic work-up. Pulmonary metastasectomy (repeated as necessary) is of paramount importance to the long-term survival of patients with nonrhabdomyosarcomatous soft-tissue sarcomas—which are generally less chemosensitive than rhabdomyosarcoma. Metastasis to the lymph nodes is rare (3.9%) and is related to the grade of the primary tumor.[6]
In our experience, documented nodal metastasis was found in only 9 of 60 patients who underwent lymph node biopsy or dissection, and 7 of these 9 patients experienced high-grade (grade 3) tumors.[6] Nodal metastasis of nonrhabdomyosarcomatous soft-tissue sarcoma in adults (stage IV disease in the current American Joint Committee on Cancer staging system) has been recognized to be associated with a poor outcome[11] and is commonly treated with radical surgery. Rhabdomyosarcoma, in contrast, can spread to the lung, bone, and bone marrow. With a 10% incidence, metastasis to lymph nodes is more common, particularly in patients with primary tumors in the genitourinary system or extremities. In patients with rhabdomyosarcoma—unlike those with nonrhabdomyosarcomatous soft-tissue sarcomas—the presence of resected nodal disease (group IIb or IIc) does not increase the disease stage, because more than 50% of these children can become long-term survivors with combined-modality therapy.[12]

**Treatment**

Knowledge of the natural history and biology of these tumors is essential to their optimal primary management. Surgery remains the mainstay of therapy for nonrhabdomyosarcomatous soft-tissue sarcomas because of the lack of effective chemotherapy agents and frequent location in the extremities. A 1- to 2-cm margin of normal tissue or an intact fascial or aponeurotic layer is often needed to adequately control the disease locally. However, this goal is often difficult to achieve, especially in the deep margins adjacent to a neurovascular bundle. In our series of 121 patients with clinical group I and II disease,[3] administration of radiotherapy decreased the local failure rate for patients with group II disease. However, the status of the surgical margin or the administration of adjuvant radiotherapy did not influence the local recurrence rate among group I patients.

In cases of infantile fibrosarcoma and hemangiopericytoma—which behave differently from other nonrhabdomyosarcomatous soft-tissue sarcomas—radical surgery is not indicated. Finally, in the only randomized pediatric trial conducted to date, adjuvant chemotherapy failed to improve survival in surgically resected nonrhabdomyosarcomatous soft-tissue sarcomas.[13]

Because rhabdomyosarcoma is a highly chemosensitive tumor, chemotherapy plays a pivotal role in its management. The role of surgery often depends on the tumor site, stage, and patient’s age. Primary tumors of the head and neck can be categorized as surgically accessible (eg, scalp, external ear, cheek) or inaccessible (eg, parameningeal, nasopharyngeal). In the latter case, the surgeon’s primary role is to obtain tissue for diagnosis. There have been incidental reports of base-of-skull resection for recurrent disease and the use of myocutaneous flaps after extensive resection. In the genitourinary tract, surgery is minimized to preserve bladder function, and exenteration is reserved for treatment failure.

Debulking surgery may be helpful only to patients with embryonal rhabdomyosarcoma of the retroperitoneal region. Blakely et al concluded that the rate of 4-year failure-free survival was better when tumors in this site were debulked than when only biopsy was performed (72% vs 48%; \( P = .03 \)).[14]

Thus, because most rhabdomyosarcomas are sensitive to chemotherapy or radiation therapy, surgery is limited to initial biopsy and resection, or assessment of response after these therapies are used.

**References:**


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