Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)

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The soft tissue sarcomas other than rhabdomyosarcoma [called the non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)] account for approximately 4% of all childhood tumors and as a group are slightly more common than rhabdomyosarcoma. NRSTS arise from primitive mesenchymal cells. Most are named for the mature tissue which the tumor most closely resembles, although they often arise at sites where the mature tissue does not exist. For example, synovial sarcoma is named based on its resemblance to synovium, though it frequently arises distant from joints.

In children, the most common NRSTS are fibrosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, fibrosarcoma protuberans and undifferentiated sarcoma. Fibrosarcoma is more common in infants while synovial sarcoma and malignant peripheral nerve sheath tumor (MPNST) is more common in older children and adults. Because each of the NRSTS is individually quite rare in pediatrics, little is known about their biology or natural history; and therapeutic recommendations are largely derived from the treatment of soft tissue sarcomas in adults.

Risk Factors:

Most cases of NRSTS have no obvious cause, but some are associated with genetic and/or environmental factors. Individuals with germline mutation of the \( p53 \) gene (Li-Fraumeni syndrome), \( RB \) gene (hereditary retinoblastoma), and \( NF-1 \) gene (neurofibromatosis type 1) are at increased risk of developing NRSTS.

Exposure to ionizing radiation predisposes to the development of NRSTS, although fewer than 5% of NRSTS are radiation-related. In immunocompromised patients with HIV infection, Kaposi sarcoma is associated with infection by human herpesvirus-8, while leiomyosarcoma is associated with Epstein-Barr virus infection.

Clinical Signs and Symptoms:

Although they can develop in virtually any part of the body, about half of all pediatric NRSTS arise in the extremities. The remaining cases are relatively evenly distributed among the trunk wall, head and neck, and visceral/retroperitoneal sites. Most commonly, NRSTS presents as an asymptomatic solid mass; systemic symptoms are extremely rare except in patients with widely
disseminated disease. Local invasion of adjacent anatomical structures may produce other symptoms.

Patients may complain of pain, swelling, numbness, or loss of function, which might be due to neurovascular deficits caused by tumor invasion. Other complaints include respiratory difficulties that can be due to large chest wall tumors; and abnormal neurologic functioning due to CNS tumors. Hypoglycemia is sometimes seen with advanced hemagiopericytoma, and hyperglycemia has been observed in patients with fibrosarcoma of the lung.

Approximately 15% of patients have metastatic disease at the time of initial presentation. The lung is by far the most common site of metastasis. Regional nodal involvement is rare except in selected histologies, such as clear cell sarcoma and epithelioid sarcoma. Liver, bone, brain, and soft tissue metastases are uncommon; bone marrow involvement is exceedingly rare.

**Diagnostic Work up and Staging/Classifications**

Incisional biopsy of the tumor is the gold standard approach to diagnosis, since an adequate specimen is critical for accurate identification of histologic subtype and grade. Multiple core needle biopsies may be an adequate alternative, but fine needle aspiration cytology is inadequate. Molecular pathologic studies to detect tumor-specific chromosomal abnormalities might also be useful.

The World Health Organization system for classifying soft tissue tumors is most commonly used for diagnostic classification. This system divides tumors by clinical behavior into 4 categories: benign; intermediate, locally aggressive; intermediate, rarely metastasizing; and malignant.

Assessment of tumor grade is a critical component of the initial diagnostic evaluation, since prognosis (and therefore treatment) depends largely on this factor. Tumor grade can be assigned using the (A-3) Pediatric Oncology Group system, designed specifically for pediatric NRSTS. Alternately, a grading system used for adult soft tissue sarcomas can be used. However, systems designed for adults do not account for tumors limited to pediatric disease, such as infantile fibrosarcoma and infantile hemangiopericytoma.

**Clinical Laboratory Tests** (renal and liver function tests) should be obtained prior to initiation of treatment in patients who will receive chemotherapy.

**Imaging Studies** - The primary tumor should generally be evaluated with MRI, which provides optimal definition of local disease extent. For tumors within the chest and abdominal cavities, CT may be substituted. Imaging of regional lymph nodes is indicated for tumors associated with a significant likelihood of nodal involvement, but sentinel lymph node mapping may be more sensitive than diagnostic imaging for identifying occult nodal disease.

A chest x-ray or CT scan is obtained in all patients due to the predominance of pulmonary metastases in NRSTS. Bone scintigraphy is restricted to patients with bone pain or other sites of metastasis; liver imaging is necessary only in those with intra-abdominal and retroperitoneal tumors. Brain imaging may be restricted to symptomatic patients and perhaps to those with widespread metastatic disease.
Lumbar Tap/CSF examination is necessary only in patients with tumors arising in cranial and paraspinal parameningeal sites.

Staging:

There is no standardized clinical staging system for pediatric NRSTS, so most clinicians use the (A-4) AJCC/UICC (American Joint Commission on Cancer/International Union Against Cancer) system to categorize patients by risk. The (A – 5) surgicopathologic staging system used by the Intergroup Rhabdomyosarcoma Study for Rhabdomyosarcoma, which assesses the extent of tumor present after initial surgery, is also occasionally used.

Prognosis

(A – 6) Prognosis depends on tumor grade and size, the extent of tumor resection, and the presence or absence of metastatic disease. High risk patients include those with metastatic disease, whose likelihood of survival is in the 15% range. Intermediate risk patients have an approximately 50% chance of survival and include those with non-metastatic but unresectable tumors, and those with resectable tumors that are both high grade and > 5 cm in diameter. The outlook for low-risk patients is excellent, with survival in excess of 90%. Low-risk patients include those with resectable low-grade tumors and those with resectable high-grade tumors that are ≤ 5 cm in diameter.

Treatment

There have been few prospective clinical trials in pediatric NRSTS, so the treatment approach in children is largely derived from data in adults with soft tissue sarcomas. However, the clinical behavior of certain histologic subtypes differs from that in adults, so this approach must be used cautiously. Some therapeutic considerations may differ in childhood, where therapy may have a deleterious impact on normal growth and development. Further, patients have many decades to develop late complications such as second malignant neoplasms, so treatment must be applied judiciously. Treatment of pediatric NRSTS should be planned by a multidisciplinary team composed of pediatric oncologists, surgeons, and radiation oncologists. Outside a clinical trial setting, treatment plans should be individualized with the goal of maximizing tumor control and minimizing short- and long-term morbidity.

Surgical Management: Surgery is a mainstay of NRSTS treatment, and cure is rare if gross tumor is not excised. Therefore, the goal is to resect all sites of disease with wide margins. Repeated operations, including morbid procedures, may be necessary to achieve this goal. Neoadjuvant therapy (chemotherapy and/or radiotherapy) can be helpful in some cases to facilitate tumor resection.

Radiation Therapy is useful for achieving durable local control in patients with microscopic residual disease after surgery. However, unlike in rhabdomyosarcoma, gross tumor control by radiotherapy is very poor. Radiotherapy may also play a neoadjuvant role in shrinking an otherwise unresectable tumor to facilitate surgery. Radiotherapy must be used judiciously, given its potential for serious long-term morbidity in children. Newer techniques such as interstitial brachytherapy might achieve adequate tumor control with fewer long-term toxicities in selected cases.
Chemotherapy has not been proven to improve outcome substantially in adults with soft tissue sarcomas, so its use remains controversial. However, it has a clear place in the neoadjuvant setting for patients with unresectable tumors, where it may facilitate gross tumor resection. The benefit of chemotherapy in the adjuvant treatment of children with NRSTS is less clear, though it is likely to be most helpful in patients with non-metastatic, large, high-grade tumors who are at high risk for distant metastatic recurrence. Even in this population, its use may be appropriately restricted to histologic subtypes known to be relatively chemosensitive, such as synovial sarcoma.

**Future Directions:**

Studies aimed at improving our understanding of the biology and clinical behavior of NRSTS are underway. Although surgery remains the most important treatment modality, the roles of chemotherapy and radiation therapy are being investigated. Risk-based treatment approaches are being tested in both U.S. and European studies to determine which patients require adjuvant therapy. Further study is also needed to assess the long-term toxicity of various treatment approaches in NRSTS.
Non-rhabdomyosarcoma soft tissue tumors (NRSTS)

Helpful Web Links:

National Cancer Institute – Childhood Soft Tissue Sarcoma
http://www.cancer.gov/cancertopics/pdq/treatment/child-soft-tissue-sarcoma/HealthProfessional/page1

St. Jude Children's Research Hospital
http://www.stjude.org/disease-summaries

eMedicine – Non rhabdomyosarcomatous soft tissue sarcoma
http://www.emedicine.com/ped/topic2764.htm

Related www.Cure4Kids.org Seminars

Seminar #413 Soft Tissue Sarcoma in a 21 Month-Old
Leo Hamilton, MD, Jesse J. Jenkins, III, MD and Fredric Hoffer, MD
http://www.cure4kids.org/seminar/413

Seminar #262 Local Management of Non-Rhabdo Soft Tissue Sarcomas
Matthew J. Krasin, MD, Christine Fuller, MD and Fredric Hoffer, MD
http://www.cure4kids.org/seminar/262

Seminar #83 Metastatic Leiomyosarcoma in a child with AIDS
Sheri Spunt, MD, Jesse J. Jenkins, III, MD, Beth McCarville, MD and Jeffrey T. Sample, PhD
http://www.cure4kids.org/seminar/83

Seminar #103 Recurrent Chondrosarcoma Post-op Intensity Modulated Radiation Therapy
Najat C. Daw, MD, Sandeep Samant, MD, Jeffrey Buchsbaum, MD, PhD, Christine Fuller, MD and Kathleen J. Helton, MD
http://www.cure4kids.org/seminar/103
Appendix:

A – 1 10 Most Common NRSTS in Childhood According to SEER Registry Data –

Rhabdomyosarcoma (41.3%)
Dermatofibrosarcoma protuberans (8.4%)
Synovial sarcoma (7.7%)
Sarcoma NOS (5.4%)
Malignant fibrous histiocytoma (4.9%)
Fibrosarcoma (4.5%)
Malignant peripheral nerve sheath tumor (3.4%)
Liposarcoma (2.8%)
Epithelioid sarcoma (2.0%)
Leiomyosarcoma (1.8%)


Infantile fibrosarcoma:

This is the most common soft tissue sarcoma found in children under one year of age. It presents as a rapidly growing mass at birth or shortly after. This form of fibrosarcoma tends to behave in a more benign fashion than fibrosarcoma in older children, which behaves more like the type found in adults.

Courtesy of C. Rodriguez-Galindo, MD
St Jude Children’s Research Hospital

Synovial Sarcoma
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
http://www.hopkinskimmelcancercenter.org/kpc/sarcomasofttissue.cfm
A – 2 Factors Implicated in NRSTS

<table>
<thead>
<tr>
<th>Histology</th>
<th>Chromosomal aberrations</th>
<th>Genes involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatofibrosarcoma</td>
<td>t(17;22)(q22;q13)</td>
<td>COL1A1/PDGFB</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>t(12;15);+11; also +8,+17,+20</td>
<td>ETVG(TEL)/NTRK3</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>Deletion 17q11.2</td>
<td></td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>19p+, ring chromosome</td>
<td></td>
</tr>
<tr>
<td>Hemangiopericytoma</td>
<td>t(12;19)(q13;q13.3) and t(13;22)(q22;q13.3)</td>
<td></td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>t(x;17)(p11.2;q25)</td>
<td>ASPL/TFE3 [8,9]</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>t(12;14)</td>
<td></td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(x;18)(p11.2;q11.2)</td>
<td>SYT/SSX</td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;22)(q22;q12)</td>
<td>EWS-CHN</td>
</tr>
<tr>
<td>Clear cell sarcoma (MMSP**)</td>
<td>t(12;22)(q13;q12)</td>
<td>ATF1/EWS</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>t(12;16)(q13;p11)</td>
<td>FUS/CHOP</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumors</td>
<td>t(11;22)(p13;q12)</td>
<td>WT1/EWS [2]</td>
</tr>
<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td>t(7;16)(q33;p11)</td>
<td>FUS/BBF2H7</td>
</tr>
</tbody>
</table>

** Malignant melanoma of soft parts

National Cancer Institute

Congenital Syndromes:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes/Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckwith-Wiedemann</td>
<td>11p15, CDKN1C, IGF2, myxomas, fibromas, hemartomas, rhabdomyosarcoma, Wilms tumor, pancreaticoblastoma, hepatoblastoma</td>
</tr>
<tr>
<td>Carney Complex</td>
<td>17q23-4, PRKAR1AK, 2p16, myxomas, melanocytic schwannomas, GIST</td>
</tr>
<tr>
<td>Diaphyseal Medullary Stenosis</td>
<td>9q21-2, pleomorphic undifferentiated sarcoma</td>
</tr>
<tr>
<td>Familial adenomatous polyposis and familial infiltrative fibromatosis</td>
<td>5q21, APC, desmoids, colon cancer</td>
</tr>
<tr>
<td>Myofibromatosis</td>
<td>Autosomal recessive, myofibromas</td>
</tr>
<tr>
<td>Neurofibromatosis Type 1</td>
<td>17q11, NF1, neurofibroma, MPNST, pheochromocytoma</td>
</tr>
<tr>
<td>Neurofibromatosis Type 2</td>
<td>22q12, NF2, schwannoma, auditory neuroma</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>13q14, RB1, retinoblastoma, osteosarcoma, soft tissue sarcomas</td>
</tr>
<tr>
<td>Rhabdoid predilection Syndrome</td>
<td>22q11, SMARCB1, rhabdoid tumor, atypical teratoid/rhabdoid tumor</td>
</tr>
<tr>
<td>Rubenstein-Taybi Syndrome</td>
<td>Myogenic sarcomas</td>
</tr>
<tr>
<td>Werner Syndrome</td>
<td>8p11-12, WRN, bone and soft tissue sarcomas</td>
</tr>
</tbody>
</table>

A-3 Pediatric Oncology Group (POG) Grading System for STS other than Rhabdomyosarcoma

Grade 1 –

- Myxoid and well-differentiated liposarcoma
- Deep-seated dermatofibrosarcoma protuberans
- Well-differentiated or infantile (age <5 years) fibrosarcoma
- Well-differentiated or infantile (age <5 years) hemangiopericytoma
- Well-differentiated malignant peripheral nerve sheath tumor

Grade 2 –

- Sarcomas not specifically included in grades 1 or 3 and which have a mitotic index of < 5 per 10 high power fields (hpf), using a 40X objective,

  - < 15% of the tumor shows geographic necrosis

  - Low cellularity and absence of significant pleomorphism are secondary criteria that can be used in assignment of borderline cases.

Grade 3

- Pleomorphic or round cell liposarcoma
- Extraskeletal mesenchymal chondrosarcoma
- Extraskeletal osteosarcoma
- Malignant triton tumor

- Sarcomas not specifically in grade 1 and which have amitotic index of >4 per 10 hpf or in which > 15% of the tumor show a geographic necrosis.

  - High cellularity and significant pleomorphism are secondary criteria that can be used in assignment of borderline cases.
Non-rhabdomyosarcoma soft tissue tumors (NRSTS)

A – 4 American Joint Commission on Cancer (AJCC) Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor (T)</th>
<th>Node (N)</th>
<th>Metastasis (M)</th>
<th>4 tiered Grading**</th>
<th>3 tiered Grading**</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1a, 1b, 2a, 2b</td>
<td>N0</td>
<td>M0</td>
<td>G 1-2</td>
<td>G 1</td>
<td>Low</td>
</tr>
<tr>
<td>Stage II</td>
<td>T1a, 1b, 2a</td>
<td>N0</td>
<td>M0</td>
<td>G 3-4</td>
<td>G 2-3</td>
<td>High</td>
</tr>
<tr>
<td>Stage III</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>G 3-4</td>
<td>G 2-3</td>
<td>High</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any G</td>
<td>Any G</td>
<td>High or Low</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N0</td>
<td>M1</td>
<td>Any G</td>
<td>Any G</td>
<td>High or Low</td>
</tr>
</tbody>
</table>

** 4 tiered system: Grade 1 and 2 = Low; Grade 3 and 4 = High
3 tiered system: Grade 1 = Low; Grade 2 and 3 = High

Definitions:

T -- Primary tumor

| TX | primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor 5 cm or less in greatest dimension |
|   | T1a superficial tumor |
|   | T1b deep tumor |
| T2 | Tumor more than 5 cm in greatest dimension |
|   | T2a superficial tumor |
|   | T2b deep tumor |

- Superficial tumor located exclusively above the superficial fascia without invasion of the fascia
- Deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.
- Deep tumor classification also includes retroperitoneal, mediastinal, and pelvic sarcomas.

N – Regional Lymph Nodes

| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

M – Distant Metastasis

| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis present |

G – Histologic Grade

| GX | Grade cannot be assessed |
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |
| G4 | Poorly differentiated or undifferentiated |
A -5 Intergroup Rhabdomyosarcoma Study Surgicopathologic Staging System

Clinical Group I: Localized disease, completely resected
  a. confined to muscle or organ of origin
  b. contiguous involvement – infiltration outside the muscle or organ of origin, as through fascial planes

Clinical Group II: Total gross resection with evidence of regional spread
  a. grossly resected tumor with microscopic residual disease
  b. regional disease with involved nodes, completely resected with no microscopic residual
  c. regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection.

Clinical Group III: Incomplete resection with gross residual disease
  a. after biopsy only
  b. after gross major resection of the primary (>50%)

Clinical Group IV: distant metastatic disease present at onset

  Lung, liver, bones, bone marrow, brain and distant muscle and nodes. The presence of positive cytology in the cerebrospinal, pleural or abdominal fluids, as well as implants on pleural or peritoneal surfaces, are regarded as indications for categorizing the patients in this group.
A – 6  Estimates of survival of patients with initially resected, initially unresected, and metastatic NRSTS treated at St Jude Children’s Research Hospital


Acknowledgments:

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