

Pediatric Sarcomas: Diagnosis and Management



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Sarcomas are a heterogeneous group of malignant connective tissue tumours that arise in bone and soft-tissue sites throughout the body. Primary bone sarcomas in pediatric patients consist of two main entities, osteogenic sarcoma and Ewing sarcoma, and account for approximately 5% of all cancer diagnoses in children and adolescents. By comparison, the soft tissue sarcomas constitute many distinct entities, as categorized by the World Health Organization, that typically resemble a normal mesenchymal tissue counterpart. Rhabdomyosarcoma (skeletal

muscle origin) is the most common soft-tissue sarcoma diagnosed in children under 10 years of age. In the adolescent and young adult cohort, it is more common to diagnose one of the many subtypes of non-rhabdomyosarcoma soft tissue sarcomas including synovial sarcoma, pleomorphic sarcoma and malignant peripheral nerve sheath tumour. Overall, bone and soft tissue sarcomas make up approximately 10-12% of all pediatric and adolescent cancer diagnoses.

Figure 1

Clinical Presentation

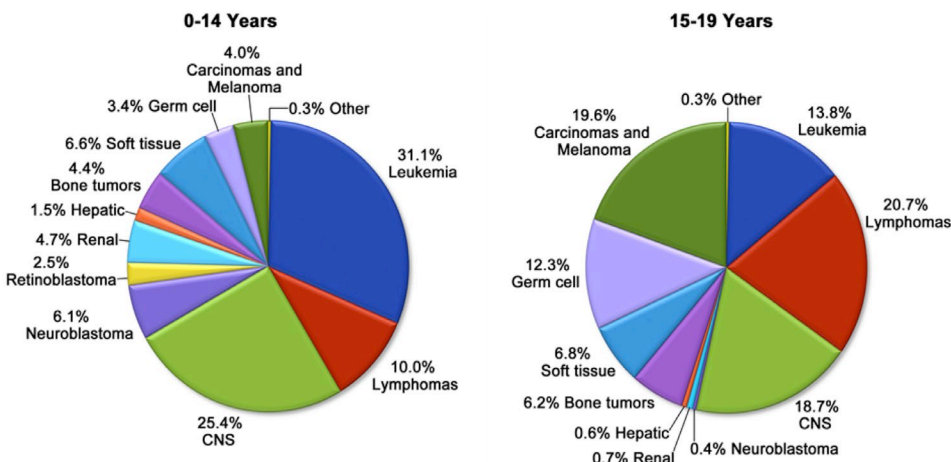
Because of the heterogeneity of bone and soft tissue sarcomas, patients may present to a clinician's attention in a variety of ways. In general, bone sarcomas present with pain, dysfunction and/or enlarging mass localizable to the bone of origin.

Osteosarcomas are most often diagnosed in the long bones of the appendicular skeleton (most commonly distal femur) and Ewing sarcomas in bones of the axial skeleton (most commonly pelvis). The signs and symptoms of a patient with a soft tissue sarcoma depend on the site of the primary lesion (pain, dysfunction, mass effect) and presence of any metastases. In all cases of sarcoma combined, the most common site of metastasis is to the lungs. Patients with bone and soft tissue sarcomas may or may not present with constitutional symptoms including fevers, weight loss, appetite change and night sweats.

Most patients develop bone and soft tissue sarcomas sporadically – that is, with no identifiable cause, no strong family history of malignancy and no known genetic predisposition to cancer. In rarer cases, clinicians may suspect, and be actively screening for, the occurrence of a bone or soft tissue sarcomas in their pediatric patients with a known hereditary cancer predisposition syndrome. One such entity to highlight in a discussion of pediatric sarcomas is Li-Fraumeni Syndrome (LFS). This autosomal dominant genetic disorder results in alteration of the tumour suppressor gene p53 and subsequent predisposition to multiple episodes of multiple tumour types in a patient's lifetime. Features of Li-Fraumeni syndrome include positive cancer history in multiple family members, particularly those diagnosed at a young age, with certain tumour types. The most common

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Figure 1: Age-Adjusted and Age-Specific Cancer Incidence Rates for Patients 0-19 Years of Age (SEER 2005-2009)



Local reference: <https://www.healthlinkbc.ca/health-topics/ncidrooooo62872>



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malignancies seen in patients with p53 mutations include osteosarcoma, rhabdomyosarcoma, adrenocortical carcinoma, breast carcinoma and various brain tumours. In a person with LFS, the cumulative incidence of cancer by the age of 50 is approximately 65% in males and 90% in females. This exceedingly high risk makes surveillance and early detection of tumours important. Oncologists at Sickkids Hospital in Toronto have shown that very specific surveillance program with routine clinical examinations, brain and body MRI, ultrasound, bloodwork and other specific radiologic testing can help to improve survival in patients with LFS (Villani et al. 2011. Lancet Oncology).

Diagnosis and Staging

Many radiographic modalities are used in the diagnosis and staging of a patient with suspected sarcoma. When an osseous lesion is suspected, a radiograph in two planes should be part of the initial diagnostic evaluation. Plain x-rays may be less helpful in the case of soft tissue sarcomas. Next, cross-sectional imaging of the primary lesion with computed tomography (CT) or magnetic resonance imaging (MRI) is done to obtain three dimensional measurements (this is of prognostic importance in soft tissue sarcomas) and to illustrate the effect of the lesion on surrounding organs and neurovascular structures. Staging work up commonly includes CT scan of the lungs and either bone scan or positron emission tomography (PET) scan depending on local protocols. Many of the Children's Oncology Group (COG) trials are investigating the role and utility of PET scan in the diagnosis, staging and follow up of sarcoma patients. Because patients with suspected sarcomas receive a number of scans it is important for community sites and tertiary centers to strive for a coordinated approach to minimize unnecessary radiation exposure and sedations. On a case by case basis, further staging evaluations may include bilateral bone marrow studies and/or lumbar puncture.

While radiographic tests will describe the location and extent of primary sarcoma

lesions and any metastatic disease, they are limited in their ability to diagnose any specific malignancy by name. Therefore, pathologic analysis of a biopsy or resection specimen is an important step in the diagnostic work up of these patients. Our pathology colleagues use histological, immunohistochemical and, more recently, cytogenetic/molecular techniques to precisely diagnose individual entities on the wide spectrum of bone and soft tissue sarcomas. Cytogenetic alteration, commonly chromosomal translocations, can greatly assist in the diagnosis and prognostication process. EWS gene rearrangements on chromosome 22, most commonly translocation EWS-FLI1, occur in greater than 95% of Ewing sarcoma family of tumours. Similarly, work by Dr. Poul Sorensen at the BC Cancer Agency documented a translocation between chromosome 12 and chromosome 15 resulting in ETV6-NTRK3 fusion now used to diagnose and distinguish infantile fibrosarcoma from adult forms of fibrosarcoma. In rhabdomyosarcoma alterations involving the FOXO1 locus on chromosome 13 (PAX3/FOXO1; PAX7/FOXO1) indicate a poorer prognosis and may be more important than alveolar vs. embryonal histology when it comes to prognostication and risk stratification.

Treatment

Once the diagnosis of a bone or soft tissue sarcoma is made, treatment planning begins immediately. The main goal of treatment is to achieve local control of the tumour(s) using surgery, radiation or both. Generally speaking, the role for chemotherapy is for the control of macroscopic or microscopic metastases. This multimodality approach to the management of sarcomas has been studied and improved upon by way of collaborative group clinical trials as was discussed in the Spring 2016 Newsletter. Through these clinical trials, significant improvements in outcomes have been seen for patients with sarcomas as a whole. For example, as a result of the COG trial AEWS 0031 it was demonstrated that interval compressed chemotherapy (given every 2 weeks instead of every 3 weeks) significantly improves event free and overall survival in

localized Ewing Sarcoma patients. This is now the standard of care for such patients. Unfortunately, despite many series of clinical trials over the past few decades, the prognosis for patients with metastatic or recurrent sarcomas remains very poor.

Effective multimodal treatment of bone and soft tissue sarcomas necessitates excellent care by a multidisciplinary team. A physician team consisting of specialists from pediatric oncology, radiation oncology, surgery, pathology and radiology is required. Further, the importance of the allied health team for these patients must be highlighted. Physiotherapy and occupational therapy, dietetics, social work, child life and spiritual care are some of the services integral to the best management of the supportive care and psychosocial needs of these complex patients and their families.

Post Treatment

While we are encouraged by improvements in the survival of many patients with sarcomas this comes at the cost of late effects of treatment in a large number of survivors. These long term effects of treatment are a result of chemotherapy and can be exacerbated by having had combination treatment with radiation and/or surgery. These patients require not only ongoing surveillance for recurrence of the sarcoma but a multisystem screen for long term toxicities. Among the body systems most affected are the heart (anthracyclines, radiation), kidneys (alkylators, radiation) and gonads (alkylators, radiation). It is well known that fertility for both male and female survivors of sarcoma therapy can be significantly impacted. Oncofertility is a field that is starting to gain awareness and momentum with multidisciplinary care involving pediatric oncologists, endocrinologists, gynecologists, urologists and specialists in reproductive medicine. Survivors may also develop second malignancies as a result of exposure to chemotherapy (etoposide, alkylators) and radiation. A well established late effects clinic exists at BC Children's Hospital but long term follow-up for survivors of childhood cancer is also done at satellite and community sites.

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LEAF Clinic opens for adult survivors of childhood cancer

Adult survivors of childhood cancer in BC now have the expert care and follow-up their health requires thanks to the establishment and opening of the BC Cancer Agency's Late Effects Assessment and Follow-up (LEAF) Clinic this summer. The Clinic is part of the broader Adult Childhood Cancer Survivors Program at BC Cancer Agency, and is located in Vancouver, serving the entire province of BC. The Clinic is the result of substantial effort and commitment of many of these survivors and their families, as well as the medical teams who cared for them.

The staff at the LEAF Clinic : Dr. Karen Goddard, radiation oncologist, BC Children's Hospital and BC Cancer Agency, Kimberley-Anne Reid, Nurse Practitioner , and Beverley Biggs, Counselor share their insights here.

What is the need for this clinic on a population basis?

On average, 10,400 North American children will develop cancer each year and, thanks to multiple treatment modalities and improved care, over 80% will be long-term survivors. There are approximately 3000 such survivors in BC diagnosed with childhood cancer since 1970 who are now adults. Depending on the treatment they received, these patients are at differing levels of risk for late effects including physical problems such as organ damage and secondary tumours, and psychosocial problems such as depression, anxiety and neuro-cognitive challenges.

What are the plans to reach out to patients who may not know they are at risk?

The LEAF Clinic has started a comprehensive recall program and is attempting to connect with every adult childhood cancer survivor so that we can assess and monitor their health for late effects and provide the best care possible going forward. Primary care providers can play an important role in helping to identify and refer such patients whose records may not have been maintained, but for whom monitoring is still important.



The LEAF Clinic welcomed its first patients. Team members left to right: Dr. Karen Goddard, Medical Director, Beverley Biggs, Counselor, and Kimberley-Anne Reid, Nurse Practitioner.

What types of services will be provided at the LEAF Clinic?

The Clinic provides both medical and psychosocial support. Medically, each patient's past cancer diagnosis and treatment is reviewed and their health problems are assessed. Future risks are also discussed and a surveillance and treatment plan is prepared. Investigations are then ordered as needed with primary care providers and specialists receiving summary reports. The counselor meets with patients and assesses them for psychosocial issues. Advocacy and referrals are made to community and health care providers along with advice to assist with future planning.

How can patients access services of the LEAF Clinic?

Patients can self-refer, be referred by their family physician, by BC Children's Hospital, the BC Cancer Agency, or by an allied health/community professional. Patients

must have been diagnosed at age 17 or under, be currently over age 18, five years off of active treatment and discharged from BC Children's Hospital.

LEAF Clinic contact information

Tel: 604.877.6070
Toll Free: 1.844.667.6070
Email: ACCS@bccancer.bc.ca

Website: www.bccancer.bc.ca/health-professionals/professional-resources/late-effects-assessment-follow-up

Contact

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This newsletter highlights the new Late Effects Assessment and Follow-up (LEAF) clinic at the BC Cancer Agency that will continue the care of adult survivors of childhood cancer, particularly those at highest risk for long term effects.

Clinical Trials

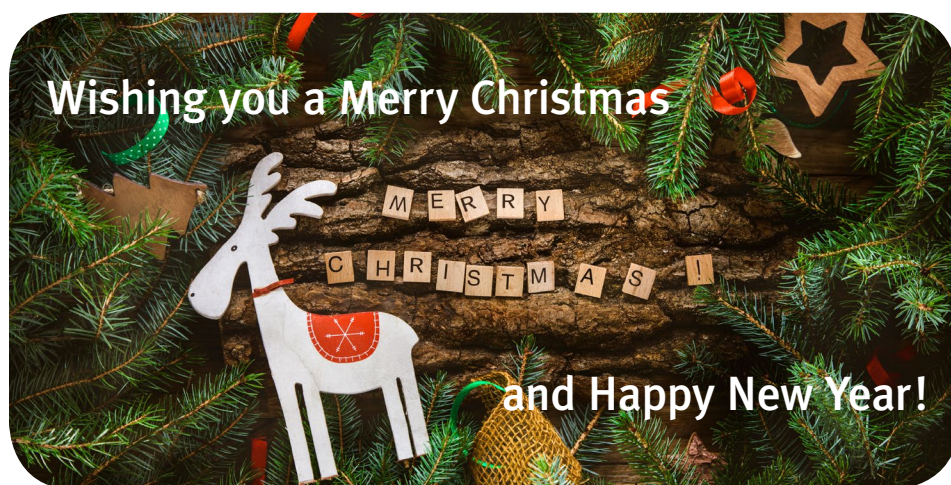
The need for new and improved treatments for metastatic and relapsed sarcoma motivates national and international cooperative groups to continue to support efforts in developmental therapeutics. The development and testing of novel treatments relies on participation in early phase clinical trials that study safety and dosing of targeted agents in patients with relapsed or refractory sarcomas. Many options for this type of trial exist at large centers in the United States but recently there have been strong efforts to make this type of study available locally for eligible patients in British Columbia. BC Children's Hospital is

currently participating in a number of Phase I and II studies available through the COG and Canadian Clinical Trials Group (CCTG). One example includes a Phase I study using Vinorelbine and Temsirolimus in Pediatric Patients with Recurrent or Refractory Lymphoma or Solid Tumours Including CNS Tumours developed and implemented by Dr. Rebecca Deyell. Enrolment of patients on clinical trials whenever possible should be considered the standard of care in cancer treatment for children, adolescents and young adults with sarcomas.

The team of oncologists focusing on sarcomas and other solid tumours is available for your reference should any questions arise about the diagnosis and treatment of any of your patients with sarcomas. Additionally, we would be happy to be a resource for information regarding clinical trials and late effect management of pediatric sarcoma patients. We thank you for your care and support of these kids and their families as they navigate a very difficult time in their lives.

The 2016 flu guidelines are posted at:

<http://www.bcchildrens.ca/Oncology-Site/Documents/Flu%20Vaccine%202016.pdf>



Our mission is to improve the health and welfare of children in BC with cancer and blood disorders through research, education, and care.

THE PROVINCIAL PEDIATRIC ONCOLOGY/HEMATOLOGY NETWORK

The Network is an interdisciplinary organization whose goal is to ensure appropriate diagnosis, management, follow-up, and end-of-life care for pediatric patients with malignancies and blood disorders.

The Network supports community hospitals and practitioners, and develops partnerships with other healthcare facilities to enable seamless and integrated care for patients and families on treatment and off treatment.

It will further develop and enhance the research programs of basic, translational, and clinical research to better childhood cancer control and improve outcomes for these patients and their families.

FOR MORE INFORMATION

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