

Issues in the Diagnosis and Treatment of Sarcomas

Sarcomas are malignant neoplasms arising in nonepithelial tissues of the body. The early manifestations of these somewhat rare tumors are commonly overlooked and the diagnosis is often delayed because they are not commonly encountered in practice. Fewer than 8,000 soft-tissue sarcomas and even fewer bone sarcomas are diagnosed annually in the United States. Sarcomas account for less than 1% of all cancers but cause 2% of cancer deaths, which emphasizes the aggressive biologic behavior and poor prognosis of this group of tumors.

Prior to 1970, the diagnosis and treatment of sarcomas was relatively straightforward. With a diagnosis of a sarcoma, treatment usually was surgery (often amputation) if the tumor, regardless of the type, was in an extremity. Much has changed since the 1970s, with marked improvements in diagnosis, imaging, and treatments.

The emphasis on accurate diagnosis and classification is one area of progress. Not only is typing the origin of the tumor important, but other evaluations may change the treatment approach. The histologic grade of the tumor can dictate radical vs functional surgery or may determine the addition of radiation therapy or chemotherapy. We now have specific markers for typing and subtyping sarcomas and for estimating the potential for metastasis. Advances in imaging techniques have also improved our

capabilities of early detection of primary and metastatic disease. The more sophisticated imaging techniques now used to assess the extent of tumor, especially related to tissue planes, have allowed us to change our surgery from ablative to limb-sparing surgery. These techniques have enabled us to find malignant tumors early and to monitor them and their response to neoadjuvant treatment. New imaging techniques also help to differentiate benign from malignant tumors and can assist us in deciding whether a lesion should be treated or monitored.

Treatment continues to change from the ablative surgery approach in the 1970s to the limb-sparing surgery of today. Radiation plays a key role in the management of soft-tissue sarcomas, and chemotherapy has a greater role in bone sarcomas. Metastatic disease from sarcomas was once treated palliatively, but patients with metastatic sarcomas can now be theoretically cured with surgical resection and is usually treated aggressively.

In this issue of *Cancer Control*, Timothy G. Sanders, MD, and Theodore W. Parsons III, MD, FACS, review the efficacy of the current imaging modalities in the diagnosis, staging, and follow-up of patients with musculoskeletal neoplasia. Although plain film radiography remains the gold standard in the differential diagnosis for bone lesions, newer imaging techniques can greatly improve the differential

diagnosis. The authors describe the use of bone scintigraphy as a screening modality and narrate the advantages and disadvantages of computed tomography. They also describe the use of magnetic resonance imaging to evaluate soft-tissue lesions and how they can aid in a differential diagnosis. Technologic advances will add to the resolution of magnetic resonance imaging and will assist us in assessing the effectiveness of the neoadjuvant treatments for musculoskeletal neoplasms.

William G. Ward, MD, Paul Savage, MD, Carol A. Boles, MD, and Scott E. Kilpatrick, MD, describe the medical advantages of fine-needle aspiration for diagnosing sarcomas. With experience and familiarity with the technique, fine-needle aspiration biopsy is correct 80% of the time in diagnosing sarcomas and related tumors. They review their own experience in more than 200 cases of fine-needle aspiration biopsies of both bone and soft-tissue tumors. The authors note that with a proper multidisciplinary program, adequate radiology, and clinical information to support the findings from the fine-needle aspiration, their diagnosis is sufficient 93% of the time to proceed with treatment. Histogenetic subtyping can be achieved in approximately 82% of these same cases. The approach should decrease the chance of field tumor contamination as well as decrease the cost of diagnosis.

Carlos A. Muro-Cacho, MD, PhD, and I researched the database of the National Library of Medicine and elsewhere for the literature relating to the genetic and molecular mechanisms in sarcomas. With this review of genetic alterations, chromosomal abnormalities, oncogene activation, tumor suppressor genes, and abnormalities in genes that control DNA repair and genomic instability, we present methods for refining the diagnosis of musculoskeletal tumors. This not only can lead to better diagnostic methods, but also can play a role in developing new treatment techniques.

Leah Strickland, MD, Carlos A. Muro-Cacho, MD, PhD, and I discuss the cell of origin of gastrointestinal stromal tumors (GISTs) that are related to the interstitial cells of Cajal rather than to poorly differentiated leiomyosarcomas, as previously thought. The prognosis, evaluation, and staging for GISTs are summarized. The malignant potential of GISTs is difficult to predict, but it can be estimated by the simultaneous evaluation of several clinical parameters, including symptoms, tumor size, and location. Most patients present with abdominal pain, but some patients are asymptomatic. The only absolute criterion for malignancy is tumor spread beyond the organ of origin at the time of diagnosis. What is particularly exciting, and extends the molecular observations in the previous paper, is that those GISTs that express *c-kit* are likely to respond to treatment with STI571, a potent inhibitor of *c-kit*.

The foot and ankle region is a common location for benign soft-tissue tumors. Sarcomas that occur in this region are often initially inappropriately treated. H. Thomas Temple, MD, David S. Worman, MD, and Walid A. Mnymneh, MD, retrospectively review their patients with malignant tumors of the foot and ankle treated over a 20-year period. When limb salvage was attempted, patients who underwent prior unplanned surgical excision had significantly more complications and more extensive surgical procedures involving flaps, and they also were more likely to require adjuvant radiotherapy than did the patients who underwent a planned surgical excision. While there were no statistical differences in the recurrence and disease-free survival between the two patient populations, the authors believe that unplanned surgical excisions of soft-tissue sarcomas adversely affects the quality of patient care.

Lastly, Christina J. Kim, MD, Chris Puleo, PA-C, Douglas Reintgen, MD, and I describe the use of hyperthermic isolated limb perfusion for extremity sarcomas. The treatment options for extremity sarcomas are amputation or limb-sparing surgery with radiation, which may produce significant morbidity and body disfigurement. Hyperthermic isolated limb perfusion is a surgical procedure for regional intravascular delivery of heat and high doses of chemotherapeutic and biologic agents to an extremity. This approach may be an attractive option in extremity sarcomas for unresectable lesions

that would otherwise require a limb amputation.

The last 30 years have greatly expanded our clinical armamentarium in terms of detection, diagnosis, and management. Further enhancements of management are likely to accrue soon from the burgeoning work on genomics and proteomics, which should provide a host of molecular targets that can be hit by designer bullets. The unfolding story of control of *c-kit* expression by STI571 in gastrointestinal stromal tumors is the first tangible result of this powerful research thrust.

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