Surgical Advances in Bone and Soft Tissue Sarcoma: 50 Years of Progress

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OVERVIEW

As the American Society of Clinical Oncology celebrates its 50th anniversary, physicians can appreciate the significant advances made in the treatment of patients with sarcoma. Historically, these rare tumors have garnered great interest in the medical profession, due to their ability to reach extraordinary size, resulting in substantial deformities and disabilities. Fortunately, advances in surgical management, which have occurred concurrently with advances in imaging, diagnostic techniques, and both local and systemic adjuvant treatments, offer patients diagnosed with sarcoma significant hope for successful treatment and the expectation of a meaningful quality of life.

At the time of ASCO’s founding in 1964, the management of a suspected sarcoma was limited, as tumors were typically quite advanced by the time they were identified by physical exam. Chest radiography and early techniques in radioisotope imaging1 could help identify patients with metastatic disease who had little hope for survival. Surgeons were called to perform open biopsies, followed by immediate radical amputation, whenever possible. Even with such an aggressive approach, expected survival after surgery for osteosarcoma was less than 5%.2 Adjuvant treatments were limited and of little proven benefit to most patients. A notable exception was Ewing’s sarcoma; already known to show sensitivity to radiotherapy (as reported by James Ewing, MD3), this tumor responded to the recently introduced agents vincristine4 and actinomycin D.5

Despite poor survival even with amputation, surgeons had already begun investigating the role of conservative “limb-sparing” surgery for low-grade tumors. Building on the early pioneering work of Dallas Phemister, MD, who introduced key concepts in limb-sparing surgery 20 years previously,6,7 Frank Parrish, MD, reported the use of large bone grafts to reconstruct defects following the local resection of bone tumors,8 while Ralph Marcove, MD, reported the use of liquid nitrogen (cryosurgery) in the treatment of primary and metastatic bone tumors.9 Surgical advances were also reported in the treatment of sarcoma metastases: Judson McNamara, MD, demonstrated that pulmonary resection for isolated metastatic osteosarcoma to the lungs was potentially curative.10

In the following decade, great strides were made on multiple fronts. Richard Nixon signed the National Cancer Act of 1971, broadening the scope of the National Cancer Institute (NCI) to more effectively carry out the national effort against cancer. The discovery of effective chemotherapy agents, such as adriamycin and methotrexate, offered new hope to patients with osteosarcoma.11 Advances in imaging included the use of angiography to evaluate tumor vasculature,12 the development of computerized axial tomography (CT scan) by Godfrey Hounsfield, CBE, FRS, MD, DSc,13 and Jaime Ambrose, MD,14 and the introduction of the technetium (Tc99m) labeled polyphosphate bone scan by Gopal Subramanian, PhD.15 All of these imaging modalities provided surgeons with new methods of visualizing the anatomy of a given tumor and its relationship to the surrounding anatomic structures within the surgical field. These advances led to an increased interest in limb-sparing surgery, driven by the increased understanding of anatomy and a new confidence in techniques for limb reconstruction. William Enneking, MD, introduced the resection-arthrodesis technique of limb salvage, using local bone grafts combined with intramedullary rods to replace and fuse the knee following limb-sparing tumor resections,16 Henry Mankin, MD, demonstrated that large defects could be reconstructed with massive homologous bone grafts (allografts),17 and Ralph Marcove, MD, reported that massive metallic implants (endoprostheses) could be used to replace the entire femur and the knee.18

During this same decade, Gerald Rosen, MD, working with Dr. Marcove, introduced the concept of preoperative (induction) chemotherapy, which enabled treatment while patients were waiting for the manufacturing of a custom limb-salvage implant.19 Donald Morton, MD, and Frederick Eilber, MD, reported on successful limb-sparing resection for soft tissue sarcomas when combined with chemotherapy and radio-
tion and began asking if amputation was always necessary for sarcomas. The same advances in imaging and chemotherapy driving limb-sparing surgery also led to further interest in surgery for metastatic disease involving the lungs. Additionally, biopsies for suspected sarcomas, traditionally performed by surgeons as open incisional procedures under anesthesia, were shown to be accurate with few complications when performed with a closed-needle system.

This ground swell of interest in limb-sparing surgery combined with skeletal reconstruction led to the foundation of the Musculoskeletal Tumor Society in 1977. Results from the first International Society of Limb Salvage (ISOLS) meeting in 1981 were later summarized by William Enneking, MD, as such: “532 resections were reported with a local recurrence rate of 18% and a surgical failure rate in reconstruction of 15% for an overall failure rate of 1 in 3 attempts.” After the 1989 ISOLS meeting, he noted: “More than 2,500 resections were reported with a combined local recurrence and surgical failure rates of 1 in 10 attempts—a remarkable decrease in the short span of one decade.” During this time, Dr. Enneking established an education program to train orthopedic surgeons in orthopedic oncology and introduced a standardized staging system for sarcomas, still in use today, that was prognostically significant.

As limb-sparing surgery became more widely accepted, surgeons began looking beyond the success of the surgery itself to critically analyze how such procedures affect the lives of patients. Paul Sugarbaker, MD, used a quality of life assessment comprised of a number of patient-specific scales to evaluate patients undergoing treatment for extremity sarcomas, showing little difference in outcomes following amputation compared with limb-sparing surgery with radiation. In 1993, Dr. Enneking published a simplified functional outcome scoring system for patients who underwent limb-sparing surgery that was subsequently adopted by the MSTS. Efforts to accurately depict patient outcomes after limb-sparing surgery continue to be developed.

Routine access to computed tomography (CT) imaging proved crucial to limb-sparing efforts; detailed imaging greatly facilitated the preoperative planning of surgical approaches and desired margins and provided precise localization of important neurologic and vascular structures. Magnetic resonance imaging (MRI), based on the Nobel prize–winning work of Paul C. Lauterbur, PhD, and Sir Peter Mansfield, BSc, PhD, FRS, was approved by the U.S. Food and Drug Administration (FDA) in 1984, giving surgeons and clinicians unprecedented noninvasive details of tumor anatomy. MRI was rapidly adopted by clinicians in the evaluation of patients with sarcomas. Multiaxial imaging with the ability to distinguish abnormal from normal tissue allowed surgeons to plan limb-sparing oncologic resections in areas of substantial anatomic complexity, such as the shoulder girdle and the pelvis. Similar progress was seen in efforts to resect retroperitoneal sarcomas, where complete resection was associated with substantial improvements in survival. Anatomic imaging also allowed surgeons to plan and perform effective oncologic resections based on sound anatomic principles for tumors of the spine.

These advances in surgical technique were matched by improvements in methods of reconstruction. Endoprosthetic reconstruction moved from unique custom implants, requiring weeks of manufacturing lead time, to modular implants, featuring off-the-shelf flexibility in matching patient anatomy with improved manufacturing quality controls. The introduction of modular implants led to a significant change in reconstructive trends away from allograft reconstruction, which was prevalent in the 1980s, toward endoprosthetic reconstruction in the 1990s. Data presented at the 2007 ISOLS meeting showed that the majority of patients with sarcoma were candidates for limb-sparing surgery, with satisfactory functional outcomes double that of amputation.

Early adopters of modular implants demonstrated that this form of reconstruction offered significant advantages, including improved patient outcomes and early return to function. Subsequent studies have reported the long-term outcomes of these implants, demonstrating excellent survival compared with custom implants while noting that mechanical failures, now rare, have been replaced by aseptic loosening and infection as the most common forms of implant failure. Recent work has focused on solving these specific issues, particularly aseptic loosening. Rapid implementation of changes has been facilitated by the modularity of implant systems as improved design concepts can be incorporated into existing proven implant systems by creating a new component(s) that joins with the existing system. Wide variations in the rate of aseptic loosening of cemented stems have been reported by various centers; mechanical factors...
and cement technique may account for these differences, with best results seen when stem sizes are matched to patient anatomy. Porous-coated uncemented stems have been introduced to avoid aseptic loosening, paralleling trends seen in total joint arthroplasty. A new method of biologic fixation, compressive osteointegration, was introduced to address stress shielding seen in total joints with mechanically rigid stems by creating significant mechanical loads directly at the implant/cortical bone junction through a novel loading mechanism. This device has subsequently been incorporated into a modular endoprosthetic system for limb salvage after tumor resection (Fig. 1).

Today, techniques and strategies designed to lower the risk of surgical site infections continue to be incorporated into routine limb-sparing surgery. The incidence of infection following massive endoprosthetic reconstruction in an oncology population is approximately ten times that seen following routine total joint arthroplasty. Host factors such as relative immunosuppression as a result of chemotherapy, effects of radiation on local tissue, and indwelling long-term central catheters, as well as surgical factors including extensive surgical approaches, blood loss requiring immunosuppressive allogenic blood transfusions, and the size of the implants required for reconstruction likely account for this elevated risk. New methods of sterile skin preparation that create a film barrier, locking skin bacteria into place have shown to substantially reduce the risk of surgical site infections. Preoperative testing and treatment of patients colonized by Staphylococcus aureus effectively reduces infections following orthopedic surgery. Heat-stable antibiotics, such as tobramycin, when added to bone cement have been shown to reduce the risk of infection following joint arthroplasty. The addition of an antimicrobial silver coating to a prosthetic stem has also shown a reduction in periprosthetic infection. Use of a dilute betadine soak of the prosthesis after implantation has also been shown to reduce the risk of periprosthetic infection. These and other innovative techniques hold promise of reducing the incidence of surgical site infections and sparing patients the devastating consequences of a periprosthetic infection following limb-sparing surgery.

Significant advances have occurred in implants designed to address unique challenges encountered in anatomically complex locations as well as in patients who are skeletally immature. Whereas allograft reconstructions may still be considered by some, the introduction of mechanically reliable implants continues to drive the adoption of endopros-
thetic reconstruction. Shoulder stability following proximal humeral resection can be improved with the adoption of a reverse total shoulder replacement articulation, originally introduced for patients with massive rotator cuff tears\(^5\) (Fig. 2). Recently published series have shown successful endoprosthetic reconstruction for segmental replacements of complex joints, such as the scapula (shoulder),\(^6\) elbow,\(^7\) acetabulum (hip)\(^8\) and ankle\(^9\) (Fig. 3). Similarly, expandable implants for patients who are skeletally immature for whom loss of growth plates would result in a significant limb length discrepancy have also seen significant advances. Originally introduced by Dr. Michael M. Lewis in 1986,\(^6\) expandable implants required multiple operative procedures to access the expansion mechanism and frequently suffered mechanical failure.\(^6\) Recent designs have incorporated noninvasive mechanisms using external electromagnetic fields, which activate the implant to incrementally expand in a controlled fashion. Examples include the use of a radiofrequency coil to

**FIG 2.** Reverse total shoulder with a glenosphere fixed to the scapula combined with a proximal humeral replacement using compression osteointegration for fixation to the humeral shaft. (Biomet Orthopedics, bio-modular shoulder system with compress compliant prestress device, Warsaw, IN.) Reconstruction was performed following a limb-sparing resection with excision of the rotator cuff for a dedifferentiated chondrosarcoma with areas of secondary high-grade osteosarcoma.

**FIG 3.** Replacement of the acetabulum and hip joint using an acetabular-replacing prosthesis fixed to the iliac wing with a constrained total hip replacement. (Stryker Orthopedics, periacetabular reconstruction prosthesis, Mahwah, N.J.) Reconstruction was performed following a Malawer type 2 pelvic resection for an intermediate-grade chondrosarcoma involving the acetabulum with extension into the hip joint.
release a compressed internal spring mechanism and a magnetic field generator to power an internal motor coupled by gears to the expansion mechanism (Fig. 4). Engineering challenges such as the durability of the internal expansion mechanism and compatibility issues with MRI remain for these implants.

Currently, advances in the surgical management and techniques for sarcomas continue to be driven by advances in imaging. New methods of nuclear imaging, such as positron emission tomography (PET) and PET/CT scanning, allow for early detection of tumor recurrence following treatment, more precise identification of metastatic disease, and determination of tumor metabolism, which can indicate the response of a tumor to induction chemotherapy. Intraoperative surgical navigation, using computerized systems integrating preoperative CT and MRI along with registered in vivo reference points, can offer unprecedented positioning of surgical instruments and localization of tumor margins hidden from direct visualization. Video-assisted thoracic surgery (VATS), as an alternative to traditional open thoracotomy, has been found to be safe and effective, with improved disease-free survival in selected patients with metastatic sarcoma of the lungs. Real-time imaging with ultrasound, CT, and/or MRI has permitted the use of closed-circuit probes to thermally ablate tumors (radiofrequency or cryoprobe ablation) as novel methods for induction treatment of soft tissue sarcomas, as well as for the palliation of otherwise inoperable metastatic sarcoma to the liver and to the lungs.

Over the last 50 years, techniques of surgical management and limb-sparing surgery have greatly improved for patients with sarcoma, while providing new options for patients with metastatic disease. However, despite these advances, overall patient survival has remained unchanged since the 1980s. One notable exception has been the discovery of the tyrosine kinase inhibitor imatinib and its ability to block the growth of gastrointestinal stromal tumors (GIST). New approaches in targeted treatment using molecular pathways specific to sarcoma cells offer hope for significantly improved patient survival and new opportunities for surgeons to help patients live with this complex disease.

**Disclosures of Potential Conflicts of Interest**

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