Dorothy Fox. *Zambezi Zebras.* Watercolor, 22″ × 30″.

The advantages and disadvantages of amputation and limb-salvaging techniques for the treatment of osteosarcoma are reviewed.

Orthopedic Surgery Options for the Treatment of Primary Osteosarcoma

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Background: *Osteosarcoma is the most common malignant primary neoplasm of bone. Orthopedic procedures are essential components in the multidisciplinary treatment of osteosarcoma. Limb-salvaging procedures offer adequate disease control comparable to the results obtained by amputations. This review discusses the advantages and disadvantages of the various types of amputations and the limb-salvaging techniques for the treatment of osteosarcoma.*

Methods: *The authors analyzed the characteristics of limb-salvaging procedures and amputations for osteosarcoma. Qualitative and quantitative studies published in the English language that are listed in the National Library of Medicine were used as the basis for this review. In addition, a review of an expandable prosthesis is included.*

Results: *Limb-salvaging techniques have acceptable rates of disease control. However, amputation remains a valid procedure in selected cases of osteosarcoma in most parts of the world. Orthopedic oncology surgeons have various materials, procedures, and techniques available to achieve disease control and improve function in patients with osteosarcoma.*

Conclusions: *The surgical management of patients with osteosarcoma is challenging. No difference in survival has been shown between amputations and adequately performed limb-salvaging procedures. Optimal tumor resection and a functional residual limb with increased patient survival are the goals of modern orthopedic oncology.*

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Abbreviations used in this paper: AKA = above-the-knee amputation, BKA = below-the-knee amputation.

Introduction

Osteosarcoma is the most common malignant neoplasm of bone.[1] It occurs most often in the bones of the lower extremities and in the humerus of young patients.[2] Due to the rapid and aggressive nature of the disease, the standard treatment for osteosarcoma was amputation of the affected limb.[3,4] However, over the past 3 decades, the prognosis for patients with osteosarcoma has changed dramatically.[5] The development of effective chemotherapy agents has reduced the incidence of metastatic disease and mortality.[6] Several studies have reported the evolution of adjuvant chemotherapy and the direct correlation with increased survival.[4] In addition, the advances in imaging and new materials and prostheses have provided the surgeon a more accurate preoperative plan and a broader range of operative alternatives. These advances have encouraged the development of better surgical techniques with less radical and definitive interventions. Orthopedic surgery and several other surgical specialties have recently proposed the implementation of minimally invasive approaches, computer-assisted surgery, and molecular medicine as appropriate treatment options. Procedures such as hip disarticulations and radical amputations contradict this current trend and have been the subject of constant study of their functional and psychologic outcomes.

Over the past several years, multiple studies have shown the results of limb-sparing excisions compared to radical amputations.[7-13] Pitfalls with limb salvage in young patients include complex, large, soft tissue defects, limb length discrepancies, and difficulties with the rehabilitation and functional outcome of the procedure. This review reports on the advantages and disadvantages of the various types of amputations and the limb-salvaging techniques for the treatment of osteosarcoma. We analyze the characteristics of osteoarticular allografts and different prostheses and materials utilized after wide radical excisions during limb-salvaging procedures. In addition, we propose several inclusion and exclusion criteria when considering limb-salvage procedures in this difficult-to-treat patient population.

Limb Amputation for Osteosarcoma

> "Extreme remedies are very appropriate for extreme diseases."
>
> *Hippocrates*

Osteosarcoma has a predilection for the metaphysis of the long bones about the knee joint and the upper extremity (Fig 1). Functional limitations in gait and pain with daily activities are often the main presenting symptoms. Osteosarcoma affects patients of all ages, predominantly young males.[1] For this reason, the goal of the available treatment modalities, in addition to limiting the anatomical extent of the disease and the occurrence of metastasis, is to restore the functional level. Surgery is a fundamental component of every treatment algorithm for osteosarcoma. Jaffe et al[14] showed that only 10% of patients with osteosarcoma (3 of 31 patients), were cured exclusively with chemotherapy. They concluded that with an overall expected cure rate of 50% to 65% with conventional strategies (surgery plus chemotherapy), the adoption of current forms of chemotherapy as exclusive treatments for osteosarcoma was unjustified. Similarly, the studies performed prior to the advent of chemotherapy showed the suboptimal results of surgery alone in the treatment of osteosarcoma. Friedman and Carter[15] stated that the type of surgical amputation did not influence survival but did affect the incidence of recurrence in patients with osteosarcoma. The overall survival rate with surgery alone was 5% to 23% at 5 years.

Historically, hip disarticulations and above- and below-the-knee amputations (AKA and BKA, respectively) have been the mainstay of therapy for patients with osteosarcoma. Recent advances in molecular medicine, the construction of better and longer-lasting prostheses and biomaterials, and the widespread use of accurate diagnostic techniques have had a definitive impact on the prognosis and therapeutic approach for osteosarcoma in patients living in industrialized countries. Limb-salvage procedures with novel megapros-

Fig 1. — Osteosarcoma of the distal femur.

theses and the use of allograft materials have spared young patients from the psychologic, anatomical, and functional limitations associated with amputations.[16] However, with 80% of the world population living in developing countries according to the World Health Organization, the widespread availability of these state-of-the-art techniques is limited and expensive.[17,18]

Young patients have different ways to cope with the loss of a limb due to cancer. Kagen[19] reported that children with amputations had a quick acceptance of limb loss compared to a prolonged and emotionally complex rehabilitation in patients with limb-salvaging procedures. Felder-Puig et al[20] analyzed the quality of life and psychosocial adjustment of young patients after treatment of bone cancer. They stated that psychosocial adjustment was determined by the age of the patient at diagnosis and not by the type of procedure (amputation or limb-sparing surgery) or resultant physical function. Skeletal maturity has also been proposed as an additional potential determinant of psychosocial sequelae due to its importance in determining the extent and type of the surgical procedure (eg, amputation, rotationplasty, expanding prosthesis). Overall, few randomized multicenter studies have attempted to describe the psychosocial functional level of survivors of pediatric bone tumors.[20,21] Furthermore, the studies that are available in the literature show conflicting or inconclusive results, and no consensus has been reached regarding the real psychologic impact of either amputation or limb-salvage techniques.

In developing countries, the choice for amputation over limb salvage is straightforward. Limb-salvage surgery requires high-level infrastructure such as an experienced multidisciplinary team of surgeons and oncologists, high-quality prostheses, a good tissue bank for allografts, adequate blood bank and blood product transfusion protocols, and state-of-the-art intensive care facilities. These conditions are difficult to find in such regions of the world. Of note, several attempts have been made to provide evidence-based medicine to underserved patient populations. Agarwal et al[22] described to great extent the complexity of limb-salvage procedures in developing countries.

In industrialized countries, the incidence of amputation due to malignancy has decreased from 0.62 per 100,000 people in 1988 to 0.35 per 100,000 people in 1996.[23] In a large multicenter study, Bielack et al[24] reported that the use of ablative surgery (defined as amputations, disarticulations, and rotationplasties) decreased from 60.1% (455 of 757) in the 1980s to 31.4% (265 of 844) in the 1990s. The standard of care in orthopedic oncology has been to reserve amputations for tumors with significant neurovascular involvement and poor distal extremity function. Additional indications for amputation include failed attempts at limb salvage and/or persistent local recurrence of the disease. Soft tissue contamination due to pathologic fracture or a poorly performed biopsy might also be adequate indications for amputation, especially in the presence of extensive secondary hematomas.[4,11,25]

Controversy exists regarding the advantages and disadvantages of performing an AKA vs a BKA.

An AKA can be performed through the distal femur (supracondylar), the midfemur (diaphyseal), or just below the lesser trochanter (high AKA). The ideal level for an AKA will provide a stump long enough to act as a lever arm for locomotion while allowing adequate clearance of the knee for jointed prostheses. Typically, a bone segment 15 cm above the tibial plateau or 25 cm below the greater trochanter has been described as optimal.[26] The shortest stump recommended in the available literature measures 15 cm from the greater trochanter to the level of the femoral osteotomy. However, the majority of the studies regarding AKA and BKA involve patients with infection and/or vascular insufficiency. The patient population undergoing amputation for osteosarcoma requires extensive bone and soft tissue resections, and some of the above-mentioned parameters are not always feasible. In selected cases, hip disarticulations are preferred to high AKAs.

Compared to healthy individuals, patients undergoing AKA will walk 43% slower and will expend 52% to 124% more kJ per minute.[27] Loss of the knee joint leads to inefficient gait, and patients with little or no physical reserve might lose the ability to walk again. Contributing to this problem is the abduction of the femur. The normal anatomic and mechanical alignments of the lower limb have been well defined.[28-30] In bipedal locomotion, the mechanical axis of the lower limb runs from the center of the femoral head through the center of the knee to the midpoint of the ankle.[30] This normal femur adduction allows the hip stabilizers (gluteus medius and minimus) and abductors (gluteus medius and tensor fasciae latae) to function normally and reduce the lateral motion of the body, resulting in an energy-efficient gait. Patients with an AKA have an obvious alteration of the mechanical and anatomic alignment; the residual femur is no longer aligned with the tibia, leaving the femoral shaft axis in abduction. This abduction of the femur is a result of the unopposed abductor mechanism and explains the increase in metabolic expenditure and the functional imbalance of patients undergoing AKA. Metabolic and biomechanical compromises appear to be the main pitfalls of the procedure.

The preservation of the extensor mechanism and the function of the knee joint are clear advantages of a BKA. The level of amputation is inversely proportional to the degree of independent functional living after surgery.[31] Ideally, 12 to 18 cm of tibia is required for optimal prosthetic fitting, but even a very short BKA that retains the tibial tubercle will preserve knee extension by the quadriceps muscle. Compared to AKA, where hip flexion and abduction contractures are frequently seen, BKA has a relatively common occurrence of knee flexion contractures.[32] BKA patients also have increased energy expenditure and slower gait compared to normal individuals. However, these changes are not as significant in patients with AKA. The lower energy cost and greater speed of ambulation for the BKA patient further support the importance of sparing the knee joint whenever possible.[32]

Before initiating the discussion on limb-salvage techniques, a brief description of a classic procedure is needed. The Van Nes rotationplasty, a procedure described in 1950 for the treatment of proximal focal femoral deficiency,[33] is occasionally indicated for the treatment of failed reconstructions of distal femoral tumors.

The Van Nes rotationplasty is an alternative for skeletally immature individuals in which the goal is to preserve function. When an AKA is indicated, a "more functional" limb that will act as a BKA can be obtained with this procedure. During the rotationplasty, all but the most proximal aspect of the femur is resected. The tibia is then externally rotated on the axis of the neurovascular bundle, and finally an arthrodesis of the proximal part of the femur and the tibial plateau is performed. The result is an extremity with the appearance, dimensions, and functional potential of a BKA. To achieve this purpose, the ankle is rotated 180° so that it can serve as the new "knee joint" and the attached foot, now pointing in the "wrong" direction, acts as the stump for fitting a prosthesis (Fig 2).[34]

Lindner et al[35] studied 136 patients with a high-grade osteosarcoma treated with limb salvage (79), Van Nes rotationplasty (21), or amputation (33). The patients were followed for a mean of 43 months. The authors concluded that the functional result of the Van Nes rotationplasty was superior to that of amputation or limb salvage. Of the 32 endoprosthetic reconstructions, 20 were followed by a major complication, and 6 of the prostheses were removed. Twenty of the 39 allografts were associated with a major complication, and 6 had to be removed, primarily because of fracture or infection. Of the 21 patients with a rotationplasty, 10 had a major complication, but none required an amputation. The functional results are adequate, and there have been no measurable adverse psychologic outcomes.

Fig 2. — Postoperative result of a Van Nes rotationplasty.

Limb-Salvage Procedures for Osteosarcoma

"Walking is man's best medicine."
Hippocrates

Before the mid-1970s, patients with high-grade osteosarcoma were treated with surgery only, which was usually an amputation. The limitations in imaging modalities and the incipient advances in molecular medicine and pharmacology made it difficult to assess the real size of the tumors and the grade of extension beyond the cortices. Campanacci and Laus[36] proposed predetermined levels of amputation for the common presentations of osteosarcoma, emphasizing the danger of conservative surgical margins. Even with this radical surgical approach, the mortality of patients before the advent of chemotherapy and more advanced imaging and surgical techniques was close to 80% at 5 years.[36] Multiple recent studies have shown that limb-salvage procedures are preferred to radical amputations in industrialized countries. Simon et al[25] published the first evidence-based study supporting the benefits of limb-salvaging procedures for the treatment of bone tumors. Their multicenter study, which included 227 patients with osteosarcoma of the distal end of the femur, reported the rates of local recurrence, metastasis, and survival. Three groups of patients where studied: patients in group 1 had a limb-sparing procedure, patients in group 2 had an AKA, and in group 3, a hip disarticulation was the procedure of choice. The Kaplan-Meier curves of the patients who survived and the percentage of patients without recurrent disease showed no statistical difference among the three surgical groups after a mean length of follow-up of 5.5 years (Mantel-Cox test: P=.8). Limb-salvage surgery was as safe as an amputation in the management of patients with high-grade osteosarcoma.

One critical aspect in limb-salvage procedures is achieving a complete resection of the tumor with an adequate margin. In a classic study performed at the Istituto Ortopedico Rizzoli, Gherlinzoni et al[37] characterized the different relevant margins in the treatment of osteosarcoma. Surgical margins are defined as intralesional, marginal, wide, and radical. An intralesional margin is created if the tumor is entered at any point during surgery. A marginal margin is created when the dissection extends into or through the reactive zone that surrounds the tumor. A wide margin is created when the reactive zone is not entered and the entire dissection is performed through healthy tissues. A radical margin is created when the entire bony or myofascial compartment or compartments containing the tumor is resected.

Controversy exists about what constitutes an adequate margin.[38] For high-grade sarcomas, a wide margin is considered adequate and will achieve successful control of the primary tumor in nearly 95% of cases. Marginal and intralesional margins are associated with frequent local recurrence, and the reconstruction with limb-salvaging options should be carefully considered. However, inconsistencies in the definitions and the reporting of these data can make determinations difficult, although several studies supported by the Musculoskeletal Tumor Society discuss the importance of surgical margins in the treatment of sarcomas. Virkus et al[39] revisited the classical study of Enneking and Maale[40] regarding the relevance of surgical margins in the incidence of tumor recurrence and overall survival. The authors concluded that although inadvertent contamination of the remaining tissue by tumor is suboptimal, good oncologic results still can be achieved. In addition, they stressed that it has not been shown definitively that local recurrence has an effect on overall patient survival. From the results of their study, patients with contaminated resections (suboptimal margins) do not necessarily require an amputation.[39]

Limb-salvage procedures can be divided into two groups: arthrodesis or arthroplasty.[41,42] An arthrodesis is usually obtained using bone allografts,[41,43,44] vascularized autografts,[45] or both. An arthrodesis provides a stable, durable reconstruction, resistant to physical stress and activity and requiring limited postoperative follow-up. In addition, once the allograft heals, patients seldom require additional surgical procedures. The disadvantages include the loss of knee extension with alterations in gait and function such as rising from a chair and social sitting (eg, airplane, bus, theater), an increased energy expenditure, and the additional abnormal mechanical stress to the hip and spine.

An arthroplasty preserves the joint. This can be accomplished with an allograft[43,44,46,47] or a metallic prosthesis.[48-50] The use of structural cadaveric allografts for reconstruction of large bone defects after tumor resection is a common treatment option. Lewis[6] stated that for clinicians who do not have a ready supply of allografts, a valid option is to reimplant an autoclaved tumor-bearing bone. Khattak et al[51] reported on 19 patients with wide excisions followed by reimplantation of the resected bone after autoclaving at 120° C for 10 minutes. The most common complication was infection. The autoclaved osseous segment united with the normal bone in 11 of the 12 patients at a median of 24.2 months. No patient had fracture or resorption of the autoclaved fragment. This approach constitutes a cost-effective alternative to allografts. Traditional reconstruction with avascular allografts and local tissue flaps has resulted in significant morbidity.[52,53] Complications of allografts include a high rate of infection, nonunion, and fracture that leads to failure in approximately 50% of cancer cases.[54] Several studies have shown that microvascular-free fibula transfers are an adequate method of reconstruction for long bone defects after wide en bloc resections for long bone sarcoma.[55,56]

An additional technique for salvaging the proximal part of the femur, the proximal part of the tibia, and/or the proximal aspect of the humerus is the use of an alloprosthetic composite. The procedure restores bone stock, and it provides a biologic anchor for attachment of the host tendons. These reconstructions have the potential for improved functional outcome when compared with reconstruction with an endoprosthesis alone. Farid et al[57] studied 52 patients who received a

Fig 3. — Radiographic appearance of a femoral tumor prosthesis.

proximal femoral endoprosthesis and compared them to 20 patients with an alloprosthetic composite reconstruction. The most significant finding was greater abduction strength in the patients who had the allograft-prosthetic composite reconstruction. In addition, more patients who received the alloprosthetic composite were able to walk without assistance and without a limp compared with the patients who received the endoprosthesis. Several studies of new materials and devices have shown that an allograft composite is not always necessary to achieve a tendon-prosthesis interface. The properties of porous tantalum as an effective osteoconductive metal to treat nonvascularized bone was reviewed by one of us (G.A.M.).[58] More recently, Reach et al[59] reported a resistant biologic in-growth of tendon into a porous tantalum implant surface. In a controlled animal model, their results demonstrated the potential utility of highly porous metals as biomaterials for soft tissue reconstruction. The ability to achieve tendon and bone in-growth directly into metallic devices will favor the development of novel and more physiologic oncology implants.[59]

Endoprosthetic reconstruction is performed with the use of modular oncology prosthesis (Fig 3). The modularity gives the surgeon the opportunity to restore the length of the limb in the operating room, matching the amount of bone resected. Modularity has resulted in increased availability and decreased cost. Early metal designs were custom made, resulting in obvious manufacturing delays between diagnosis and reconstruction; consequently, intraoperative flexibility was limited. Osteosarcomas are dynamic tumors that change with time and treatment. The metallic prosthesis can be fixed to the bone with polymethylmethacrylate or a press-fit porous stem can be used instead. The joint bearing is a rotating hinge that has some freedom of movement, but it will always be more constrained than a normal knee.[60] The disadvantages include loosening, excessive wear, material failure, and stiffness.

A relatively novel technique of limb salvaging, especially in skeletally immature patients, is the use of an expandable prosthesis for patients with osteosarcoma (Fig 4). The location of these tumors in the growing areas of bone commonly mandates the removal of the affected growth plate. Subsequent continued growth in the contralateral extremity results in limb-length inequality. The distal femoral growth plate produces 1.6 cm in longitudinal growth per year. From a functional standpoint, the lower extremities should be of equal length if possible. If left untreated, limb-length discrepancies can result in low back pain and even compensatory scoliosis. Gait disturbances are also commonly observed.

Custom expandable prostheses have been in use worldwide since 1976 and in the United States since 1983. The system consists of a fixed stem with a screw or a multiple plate extension mechanism that has been described elsewhere.[16] In all of the commonly used expanding mechanisms, a surgical procedure is required for the subsequent expansions.

The Phenix Growing Prosthesis (Phenix Medical, Paris, France) was designed in the early 1980s. Wilkins and Soubeiran[61] reported on 21 expansions that were performed in 6 patients (mean lengthening at each procedure was 8 mm). There were no acute complications attributable to the lengthening procedure. Although

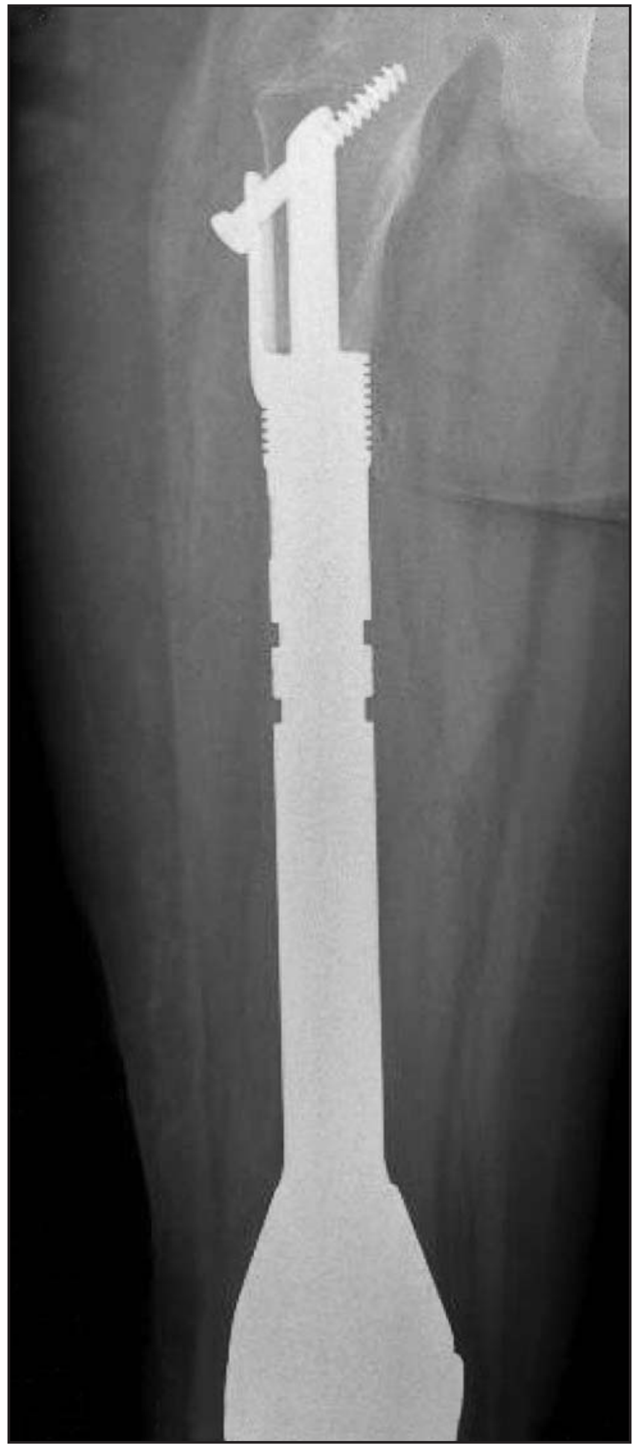

Fig 4. — Radiographic appearance of an expandable prosthesis.

this prosthesis is not frequently used at the present time, it helped spark the interest in the current models of expandable prostheses.[16]

The Stanmore expandable prosthesis (Stanmore Implants, Stanmore Middlesex, United Kingdom) has been recently introduced to the United States with a limited Food and Drug Administration approval.[62,63] When the implanted prosthesis is placed at the center of a rotating electromagnetic field, the poles of a magnet within the implant are captured, causing it to rotate in synchrony. The external field rotates at a fixed speed, causing the implant to expand at a rate of 0.23 mm per minute (1 mm every 4 minutes). Our current indication for the procedure is children who are expected to develop a limb-length discrepancy greater than 4 cm after the resection of an osteosarcoma. Currently, the only American series of patients is being followed at the H. Lee Moffitt Cancer Center in Tampa, Florida. To date, 18 lengthenings have been performed with no complications related to the procedure. Incremental lengthenings of .4 to 1.0 cm were achieved in all patients. Following lengthening, most patients walked out of the clinic and rapidly regained their motion since no surgical procedure was performed. The neurovascular status of all patients was intact both before and after the procedure. The functional results are similar to the traditional modular systems.

Conclusions

The surgical management of patients with malignant tumors of bone is challenging. Orthopedic oncology has been a dynamic specialty with countless modifications of previously accepted treatment algorithms. One of the most important paradigm changes in industrialized countries was the acceptance of limb-sparing techniques as valid alternatives to amputation. However, amputation remains as a valid procedure in selected cases of osteosarcoma and in most parts of the world.

Amputation has some unique adverse events. "Phantom" sensation, "phantom" pain, and neuroma can occur after the procedure. Additional complications include wound necrosis, bone protrusion, bone overgrowth in children, and an additional metabolic expenditure.

Although survival rates and disease-free intervals after limb salvage are comparable to those after amputation, salvage of the extremity does not always result in better function and quality of life. Limb-salvage procedures have a high rate of complications such as infection, fracture, delayed union or nonunion, joint instability, late osteoarthritis, and endoprosthetic loosening and dislocation. These complications result in a high rate of revisions and, in some cases, the need for amputation. The goal of limb-salvage surgery is to preserve a useful functioning limb without increasing the risk to the patient. The results of multiple studies available in the literature support the use of limb-sparing techniques if an adequate margin of resection is obtained. No difference in survival has been shown between the use of radical amputations and adequately performed limb-salvaging procedures.

Patient preference, tumor location and extension, comorbidities, intraoperative findings, and other variables mentioned in this review should be considered when offering an amputation or a limb-sparing procedure. Optimal tumor resection and a functional residual limb with increased patient survival are the goals of modern orthopedic oncology.

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