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REVIEW ARTICLE

Criteria and outcome of limb salvage surgery

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Summary

When sufficient margins of resection surrounding the tumor can be achieved, limb salvage surgery, as opposed to amputation, has become the standard of care in treating patients with bone and soft tissue sarcoma of the extremities. Currently, 90-95% of patients with primary malignant bone and soft-tissue tumors involving the extremities can be treated safely with wide resection and limb salvage surgery with a low risk of recurrence and the same disease-free survival rate as amputative surgery. However, discussions persist regarding the indications and criteria, and whether limb salvage provides superior functional results and quality of life for cancer patients. In this study we aimed to review and update the current criteria, indications and contraindications of limb salvage surgery and discuss its role in the quality of life of cancer patients.

Key words: indications, limb salvage surgery, quality of life, survival

Introduction

Before the 1970s, the management of patients with musculoskeletal tumors routinely consisted of amputations or disarticulations, with dismal survival rates ranging from 10-20% [1,2]. During the last 3 decades, with the development of more effective chemotherapeutic agents, radiation and combined treatment protocols, and advanced imaging and surgical techniques, survival rates have improved [1]. When sufficient margins of resection surrounding the tumor can be achieved, limb salvage surgery, as opposed to amputation, has become the standard of care in treating patients with bone and soft-tissue sarcoma of the extremities. Currently, 90-95% of patients with primary malignant bone and soft tissue tumors involving the extremities can be treated safely with wide resection and limb-salvage surgery with a low risk of recurrence and the same disease-free survival rate as amputative surgery [2-7]. Limb salvage optimizes patient satisfaction since it provides immediate mobility, stability, weight bearing, and improved quality of life in addition to the cosmetic appearance and emotional acceptance [5,8-10].

Despite these advances, however, discussions persist regarding the indications and criteria, and whether limb salvage provides superior functional results and quality of life for cancer patients [11]. In this study, we aim to review and update the current criteria, indications and contraindications of limb-salvage surgery, and discuss its role in the quality of life of cancer patients.

Criteria of limb salvage

Limb salvage surgery must be individually tailored, taking into account the underlying pathology, stage of disease, feasibility of tumor-free resection margins, and response to neoadjuvant chemotherapy [12]. The indications for limb salvage are tumors of the extremities, axial skeleton, or both, in which optimal surgical margins are achievable, soft-tissue extension is moderate, neurovascular bundles are not compromised, metastases are absent or responsive to curative treatment, and patients are in good clinical status, free of infection and compliant during treatment (Table 1) [2,12-14]. When deciding a limb salvage procedure, local

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Table 1. Indications and contraindications for limb salvage surgery [2,12-14]

Indications	*Contraindications*	*Relative contraindications*
Tumors of the extremities and/or axial skeleton. Ability to achieve tumor-free resection margins; 3 cm of normal bone around a malignant bone tumor and 1 cm of normal soft tissues. Local recurrence should be no greater and survival no worse than with amputation. The procedure, or treatment of its complications, should not delay adjuvant therapy. Reconstruction should be enduring and not associated with a large number of local complications requiring secondary procedures and frequent hospitalizations. Function of the limb should approach that obtained by amputation	Extensive local disease. Limb salvage requires complex reconstructive procedures with prolonged rehabilitation. Consequent morbidity threatens to compromise oncological treatment. Extreme age groups. Terminal appendage.	Major neurovascular structures encased by tumor when vascular bypass is not feasible. Pathological fracture with hematoma violating compartment boundary. Inappropriately performed biopsy or biopsy-site complications. Severe infection in the surgical field. Immature skeletal age with predicted leg-length discrepancy >8 cm. Extensive muscle or soft-tissue involvement. Poor response to preoperative chemotherapy.

recurrence should be no greater and survival no worse than with amputation; the procedure, or the treatment of its complications should not delay adjuvant therapy; reconstruction should be enduring and not associated with a large number of local complications requiring secondary procedures and frequent hospitalizations; and function of the limb should approach that obtained by amputation, although body image, patient preference, and lifestyle may influence the decision [14]. The ability to achieve tumor-free resection margins is imperative if limb salvage is contemplated. Optimal surgical margins around a malignant bone tumor are 3 cm of normal bone and 1 cm of normal soft tissues; however, this cannot always be obtained [13].

Contraindications to limb salvage surgery include extensive local disease, limb salvage requiring complex reconstructive procedures with prolonged rehabilitation, consequent morbidity threatening to compromise oncological treatment, extreme age groups, and end-stage cancer patients [12]. Relative contraindications to limb-salvage surgery include major neurovascular structures encased by tumor when vascular bypass is not feasible, pathological fracture with hematoma violating compartmental boundary, inappropriately performed biopsy or biopsy-site complications, severe infection in the surgical field, immature skeletal age with predicted leg-length discrepancy >8 cm, extensive muscle or soft-tissue involvement, and poor response to preoperative chemotherapy [2].

Major neurovascular structures encased by tumor

Major vascular invasion or encasement by the tumor may occur in 5% of the cases [15,16]. The decision of whether or not to resect blood vessels and to what extent depends on the preoperative imaging and intraoperative findings. Conventional angiography or duplex sonography may be necessary for improved imaging quality compared to MR angiography [16]. Modern surgical techniques and adjuvant local treatments have enabled advanced sarcomas to be resected *en bloc* with the affected neurovascular structures in cases of tumor invasion, or when vessel resection is required to obtain adequate oncological surgical margins (Figure 1). In this setting, vascular reconstruction enables a limb-sparing resection with excellent local tumor control and acceptable limb function [16-20]. However, patients who require vascular resection and reconstruction are significantly more likely to require a muscle transfer and to experience a complication including deep venous thrombosis, clinically significant limb edema and higher risk for ultimately undergoing amputation [21].

Major nerve invasion or encasement by the tumor may occur in 1.2% of the cases [15,16]. Resection of major peripheral nerves, particularly of the lower extremities, does not preclude an acceptable functional outcome if it does not create complete disability [13,15,19,20]. The goal for the lower extremities is preservation or reestablishment of plantar sensation to avoid ulcerations and injury that may lead to infection and possible amputation [19,22,23]. Patients who underwent division of the sciatic, tibial, or peroneal nerve(s) during limb salvage surgery may experience pain, phantom sensations, reduced proprioception, and foot ulcers; all these patients need an ankle brace to walk after sciatic or peroneal nerve division [15,20]. In a gait analysis study, the functional level of patients with sciatic nerve resection was inferior to that achieved by prosthetic knee replacement or rota-

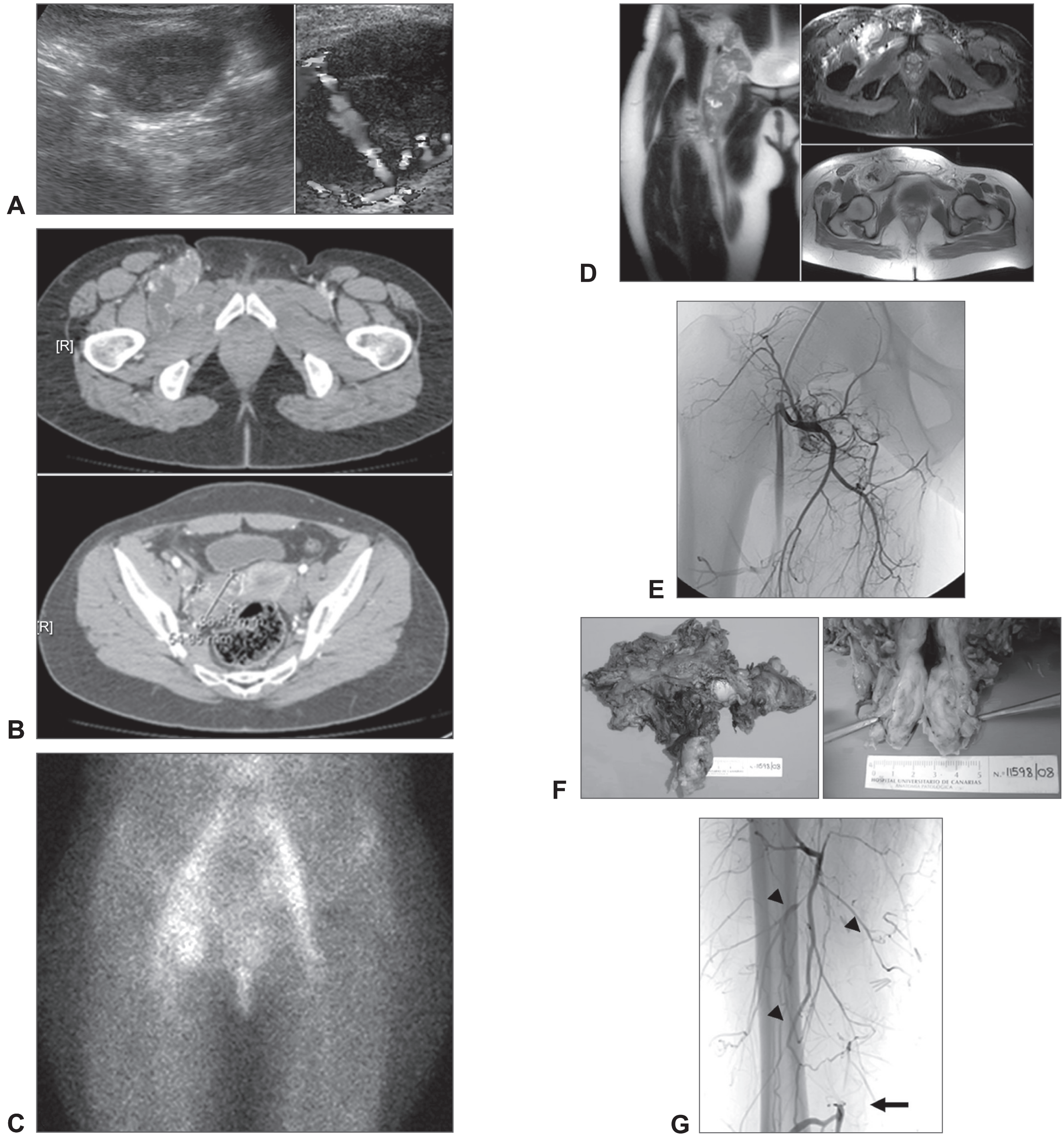

Figure 1. A 34-year-old woman with a grade IIB leiomyosarcoma of the pelvis. The patient presented with pain and palpable mass in the right inguinal area, edema and calf tenderness suggestive of deep venous thrombosis, and decreased function of her right leg. Computed tomography scan (CT) of the chest was negative for lung metastases. **(A)** Doppler (left) and triplex (right) ultrasonography showed dilation of the right common femoral, superficial femoral and popliteal veins with thickening of the walls, and partial occlusion of their lumen. **(B)** CT scan at different levels showed intraluminal thrombus and vascular neoformation at the right external iliac vein extending to the superficial and deep femoral veins. **(C)** Bone scan showed increased radioisotope uptake at the right iliac region without evidence of bone involvement. **(D)** Coronal T1-weighted (left), axial T2-weighted (upper right) and T1-weighted (down right) magnetic resonance imaging showed a soft-tissue mass measuring 14 × 5 × 4.5 cm extending to the proximal right thigh. The lesion had heterogeneous low signal intensity on T1 and high signal intensity on T2-weighted sequences with central necrosis. **(E)** Preoperative angiography showed pathological vascularization of the lesion through branches of the profunda femoris artery. Selective embolization and occlusion of the feeding vessels with N-2-butyl-cyanoacrylate was performed. **(F)** Limb-salvage surgery was decided. At surgery, the tumor was firmly attached to the femoral vein, occluding its lumen and extending into adjacent soft tissues. The tumor was resected *en bloc* with the involved vessels with wide margins. Reconstruction of the common and superficial femoral arteries with iliofemoral by-pass using a 6-mm diameter polytetrafluoroethylene (PTFE) vascular prosthesis was performed. **(G)** Angiography performed at 2 months postoperatively showed thrombosis of the vascular by-pass (arrow), however, with well-defined collateral vascularization (arrow heads) and Doppler ultrasonography wave pattern at the tibialis posterior and dorsalis pedis arteries suggesting of adequate distal revascularization. Functional outcome was satisfactory and no further treatment was applied. At 2 years postoperatively, the patient is alive without local recurrence or distant metastases; function is excellent.

tionplasty; however, the results were better than those of the patients with hip disarticulation [24]. It seems that patients with resection of the sciatic nerve at a lower anatomical level have better functional outcomes compared to patients with resections at a higher level [20].

Important sensory supply to the foot, and motor function to the posterior leg and the intrinsic muscles of the foot is provided by the tibial nerve [22,23]. Following tibial nerve resection, sensory loss on the dorsum of the foot and the plantar aspect of the forefoot and toes usually does not result in a significant functional deficit. However, loss of sensation on the entire sole of the foot frequently leads to chronic ulceration that is extremely difficult to cure [25]. In addition, an insensate sole, along with loss of the plantar arch secondary to intrinsic muscle paralysis, is tolerated poorly and frequently results in skin breakdown and ulceration. Therefore, continuity of the tibial nerve should be restored whenever possible, even if nerve grafting is required [25]. Although no significant differences between the functional scores for patients with femoral or sciatic nerve resections have been reported, femoral nerve resections are associated with falls and fractures related to absent active knee extensors, even years after surgery [26]. While musculotendinous transfer techniques for knee extension may be considered in patients with femoral nerve resection, they have not yet been explored extensively in tumor patients [26].

Due to proximal tumor locations, large nerve defect lengths, massive soft tissue defects, adult age group of many sarcoma patients, and adjuvant radiation therapy, nerve reconstruction techniques are not likely to predictably restore function after lower extremity sarcoma resections [19,27,28]. Nerve autografts have traditionally been the gold standard for nerve reconstruction, yielding favorable results and the best chance of recovery. A variety of donor nerve grafts are available including cutaneous sensory nerves such as the lateral antebrachial and the anterior division of the medial antebrachial cutaneous nerve from the upper extremity if the tumor defect is small, the sural nerve if the defect is large, and the peroneal nerve from the involved extremity for reconstruction of the sciatic nerve, allowing for partial distal sensory recovery continued protective sensation of the foot, and possible motor function [19].

On the contrary, reconstruction of the tibial nerve has a poor prognosis, especially with large defects [25,29].

Pathological fracture

The incidence of long bone pathological fracture in patients with primary bone sarcomas ranges from 5-10% [30-32]. In children and young adults, osteosarcoma and Ewing's sarcoma are the common primary bone tumors that may present with a pathological fracture [31]. In osteosarcoma, the diaphyseal location, large dimensions, osteolytic radiographic pattern, and telangiectatic and fibroblastic variants are the most important risk factors for pathological fractures [33-35]. In Ewing's sarcoma, pathological fractures have been associated with the effect of radiation therapy that further weakens the bone [30,36,37]. In the elderly, local recurrence of a primary bone tumor and secondary sarcomas including pagetic and post-irradiation sarcomas are the most common sarcomas that may present with a pathological fracture, occurring as late as 20 years after the initial diagnosis [30,37-40]. The incidence of a long bone pathological fracture in skeletal metastases has been reported between 10-29% [41-44].

In the past, the occurrence of a pathological fracture in bone sarcomas or skeletal metastases was an absolute contraindication for limb salvage; in this setting, treatment traditionally consisted of amputation proximal to the most superior aspect of the fracture haematoma [31,45,46]. Currently, the decision for limb-salvage surgery should be reconsidered [31,35-37,46-51]. No difference in outcome or local recurrence rate in osteosarcoma patients with a pathological fracture compared to that of patients without a pathological fracture has been reported; the 5-year disease-free survival was 63% compared with 61%, and the local recurrence rate was 4.3% compared to 4.8%, respectively [33]. Other authors reported that the extent of fracture displacement did not portend a poorer prognosis, nor did it necessarily predict an increased risk of local tumor dissemination or distant tumor spread [35]. The occurrence of a pathological fracture in patients with Ewing's sarcoma did not seem to be a negative prognostic factor regarding survival; therefore, a fracture at presentation should not mandate amputation if adequate local resection can be performed after appropriate non-operative treatment and chemotherapy [36,37,52].

Inappropriately performed biopsy or biopsy-site complications

Poorly performed biopsy remains a common pitfall in patients with musculoskeletal tumors who are referred to orthopedic oncology centers. An inadequately performed biopsy may fail to allow proper diagnosis, have a negative impact on survival, and ultimately necessitate an amputation to accomplish adequate margins of resection [53]. Approximately 18% of biopsies of musculoskeletal neoplasms result in an error in diagnosis, and 10% are poorly planned and executed, or result in a non-representative sample. Of greater concern, 9%

result in some sort of skin, bone, or soft tissue complication, 10% result in an alteration in the course or outcome, and 3% in unnecessary amputations. These events occur with far greater frequency and highly significant difference when the biopsy is performed in a referring institution rather than in a treatment center [53,54].

Severe infection in the surgical field and other complications

The risk of complications is related to the surgical injury, the clinical status of the patient, and the effect of adjuvant treatments [13]. Early complications associated with the extensive nature of most musculoskeletal oncology procedures include wound necrosis and dehiscence, infection, thromboembolic disease, neurapraxia, and joint instability. Infection following major limb salvage surgery for malignant tumors occurs in 10-20% of the patients [55-59]. Treatment of the infected oncological reconstruction includes implant or allograft removal and implantation of an antibiotic-loaded cement spacer, intravenous antibiotic therapy, repeat debridement and spacer change, and delayed prosthetic or allograft reconstruction and free flap coverage [60]. Yet, the amputation rate for infected oncological reconstructions ranges from 37-87% [55,61].

Immature skeletal age with predicted leg-length discrepancy >8 cm

Primary malignant bone tumors are most often encountered in children, frequently abutting the physes of long bones [12]. The knee joint is the most common location. Given that the growth plates near the knee are the most important in terms of the ultimate growth of the lower limb, children with a primary malignant tumor in the distal femur or the proximal tibia should be considered candidates for limb salvage surgery [62]. However, any surgical resection will cause a limb length discrepancy from growth plate injury and eventual functional impairment [62]. This discrepancy must be considered in conjunction with limb salvage surgery procedure and reconciled with surgical techniques to approximate equal leg lengths at skeletal maturity [63,64]. In this setting, reconstructive options for limb salvage in the skeletally immature patient have included allografts, expandable megaprostheses, and allograft-prosthetic composites [62]. Good or excellent functional scores have been reported following megaprosthetic and biological reconstructions, despite the frequent necessity for additional operations, such as limb-lengthening procedures and revision operations. Ultimate limb length discrepancy of > 2 cm has been considered substantial enough to require corrective surgery [62,65].

Extensive muscle or soft-tissue involvement

Major surgery and large bone and soft tissue defects are negative risk factors for complications following limb-salvage surgery. Wound closure and coverage of implants can be obtained with free or pedicle muscle flaps. Free flaps have several advantages over local pedicled flaps or primary closure; free flaps avoid the sacrifice of tissue from an extremity already functionally compromised by the tumor and the resection, and provide a larger volume of durable, well-vascularized tissue than local or regional flaps. However, the drawbacks of free flaps are donor site morbidity and the necessity of a skilled microsurgical team [66].

The use of reinnervated free-muscle flaps in limb-sparing surgery after resection of soft tissue sarcomas in the extremities may be indicated in young adults when radical excision of the tumor will result in severe motor functional loss.

Reinnervated free muscle flaps enable complete compartmental resection of the tumor, neglecting the subsequent reconstruction of the soft tissue defect, provide improved disease-free interval and possibly better overall survival, restore functional recovery at a higher level, and provide cosmetically acceptable skin coverage, all in one stage. The success of reinnervated free-muscle transfer requires meticulous microsurgical techniques and experienced surgeons [67].

Poor response to preoperative chemotherapy

Poor response to preoperative chemotherapy has been reported a poor prognostic factor for survival [68, 69]. However, in a study of patients with poor response to preoperative chemotherapy (necrosis >90%), the authors gave 2 preoperative courses of intra-arterial cisplatin with addition of postoperative administration of ifosfamide and etoposide to doxorubicin, methotrexate and cisplatin. The 10-year event-free survival was 67% for good responders and 56% for poor responders. At a median follow-up of 11.5 years the overall survival was 70%. The authors suggested that the prolongation of postoperative chemotherapy and the addition of ifosfamide and etoposide worked as a salvage therapy for patients who responded poorly to preoperative chemotherapy [69].

Reconstruction for limb salvage

Current options for reconstruction after limb salvage surgery consist of biological reconstructions using osteoarticular allografts and allograft-prosthesis composites, arthrodesis with intercalary bone-grafting and rotationplasty at the knee joint, megaprosthesis, vascularized fibula graft and/or interpositional allograft, extracorporeally irradiated autograft, intercalary scaffolds augmented with growth factors (tissue engineering techniques), technical refinements for tumors located close to the growth plate and distraction osteogenesis [42,55,70-78]. However, because of the extensive bone and soft tissue defects, the technically challenging and lengthy surgical procedures, the complex biomechanical reconstruction and the size of the implants, immediate and delayed implant-related complications including mechanical failure, aseptic loosening, infection, dislocation and neurovascular injury are common; failure rates of 17-33% at 5 years, and 33-52% at 10 years have been reported [4-6,79]. Despite the potential complications, megaprostheses [80-86] remain the main option for reconstruction after limb salvage surgery for bone tumors with up to 67% 10-year survival [80,87-89]. Their advantages include immediate postoperative stability, early weight bearing and rapid rehabilitation, off-the-shelf and intraoperative modularity [80,87,88,90-94]. Bone autografts are primarily indicated for children and upper extremity reconstructions following limb salvage surgery [55,72]. The use of vascularized fibula grafts is attractive but in practice, whilst bone union usually takes place, hypertrophy of the graft sufficient to allow full weight bearing can take up to 2 years, which is a major disadvantage, especially for cancer patients [73,80]. Moreover, the longer the segment to be replaced the higher the incidence of complications [73]. The combination of a vascularized fibula graft with an allograft is considered as the treatment of choice for reconstruction after limb-salvage surgery for sarcomas of the tibia [95]. In the femur, however, numerous studies have outlined the risk of complications that occur within the first 2-3 years following allograft reconstructions [55,73,89] including infection rate of 18.5-30%, delayed union or non-union rate of 30-63% [73], and fracture rate of 19-42% [89]. In addition, non-weight bearing and protective weight-bearing is necessary for up to 16 months until allograft-host bone union [96]. Moreover, the immunosuppressive effect of chemotherapy and radiation therapy, and the increased complication rates associated with these treatment options in cancer patients is well-documented [73,97]. Distraction osteogenesis is time-consuming, often limited by the large segmental defects after wide tumor resection and potentially inhibited by the side-effects and increased complication rates of chemotherapy and radiation therapy [76].

Quality of life of limb salvage versus amputation

Although current evidence suggests that patients requiring bone and soft tissue reconstruction for limb salvage can achieve good oncologic outcomes, little is known regarding the functional outcome and quality of life of bone sarcoma patients [98]. Previous studies described the function and quality of life in upper and lower extremity bone sarcoma survivors (Table 2); however, the different reconstructions, the variety of outcome measures and the short-term follow-up in these patients precludes significant conclusions [7,11,13,99-106,112,113].

The patients frequently have great concern about amputations as either a physical mutilation or causing a marked functional loss. In discussing treatment options with the patients and their families, the orthopedic oncologist should avoid introducing amputation unless this is absolutely necessary. However, amputation should not be considered the terrible curse. In respective series using questionnaires, the patients who had an amputation were as satisfied, competent and emotionally stable as patients who had limb salvage surgery [99,107,108]. Furthermore, amputation avoids the complications associated with the various reconstruction techniques used in limb salvage surgery and in many cases any concern of local recurrence [99,109]. In looking at the overall results, it is apparent that amputees seem to do as well and in some cases better with their adjustment to life as patients with limb salvage surgery. The two groups seem to have the same employment status and commitment to sports activities. They seem to walk almost equally well, although the patients with limb salvage surgery have a lesser need for walking aids. Equal percentages are married and seem to have adequate potency and sexual experiences. Both groups seem to have similar emotional responses to their surgery with small percentages of the patients having depression, anxiety, sleep disturbances, or requiring pain medication [99]. Among the amputees, below-the-knee amputation results in significantly better function than above-the-knee amputation and yields similar function as limb salvage because of limited limb loss and preservation of the knee joint [102,106,110,111]. Therefore, amputation should not be excluded from treatment of sarcoma patients and should not be considered a debilitated procedure.

Conclusion

The aim of orthopedic oncological surgery is to remove the tumor completely for local tumor control and

Table 2. Summary of reported studies on quality of life of sarcoma patients

Studies	*Outcome measure*	*Conclusions*
Aksnes et al. [106]	MSTS, TESS and SF-36	No significant difference in health-related quality of life between the amputees and the limb salvage survivors except in physical functioning, bodily pain and physical component summary scale.
Cannon et al. [112]	MSTS for the upper extremity and range-of-motion measurement	Shoulder function is suboptimal, resulting in modest function and limited active range-of-motion.
Carty et al. [7]	MSTS and TESS	Limb-salvage patients can achieve high percentage outcomes in the medium term, based on impairment and disability measures. Muscle removal was a factor related to postsurgical function suggesting that care should be taken to preserve the quadriceps musculature as much as possible.
Davis et al. [11]	TESS, SF-36 and RNLI	There was a trend toward increased disability for those in the amputation group vs. those in the limb-sparing group, with the amputation group showing significantly higher levels of handicap.
Mavrogenis et al. [113]	MSTS and TESS	The local recurrence free survival supports limb salvage surgery. The best postoperative results were achieved with respect to reduction of pain and walking ability, and participation in ordinary living activities. Hip procedures were found to have a higher mean functional score.

MSTS: Musculoskeletal Tumor Society Rating Scale; TESS: Toronto Extremity Salvage Score; SF-36: Short Form (36) Health Survey; RNLI: Reintegration to Normal Living Index

optimal survival. Current approaches combining surgical resection with radiation therapy and/or chemotherapy allow limb salvage surgery in more than 90-95% of the patients. In regard to counseling patients about their potential functional outcome we believe that limb-salvage surgery has functional and physiological benefits over traditional amputative procedures. However, limb salvage and reconstruction are associated with higher complication rates compared to amputation. To minimize complications, surgeons should choose reconstructions with which they are familiar and provide the modular options needed intraoperatively.

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