Limb Salvage Operations for Patients with Malignant Bone Tumors in the Extremities

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ABSTRACT

Neoadjuvant chemotherapy, modern imaging analyses, and developments in surgical techniques in recent decades have enabled limb salvage surgery to provide well-functioning, tumor-free, painless limbs through excision of the tumor with an adequate margin and proper reconstruction. With proper selection, patients are expected to have mostly intact body balance, a simple rehabilitation process, and an intact body image, but not at the expense of local recurrence and survival. Currently the indications of such a limb salvage procedure have been expanded to other non-malignant tumorous conditions in addition to malignant juxta-articular bone tumors in the extremities. Wide resection of a tumor can result in massive bone and soft-tissue defects. Currently, many options for reconstruction with limb salvage procedures are available, including resection arthrodesis, various bone graft techniques (vascularized or conventional autografts, allografts, or allograft/endoprosthesis composites), Ilizarov leg lengthening, rotationplasty, reconstruction with custom-made oncological endoprostheses, etc. These have resulted in expected successes, while simultaneously producing biological or prosthesis-related complications due to their unique advantages and disadvantages. The choice of an option requires careful individual considerations, including imaging radiological staging, pathological staging, and the clinical status. (***Tzu Chi Med J*** 2005; **17**:389-396)

Key words: limb salvage operation, bone graft, modular oncological endoprosthesis, complications, endoprosthetic reconstruction

INTRODUCTION

Conventional amputation of a limb with a primary malignant bone tumor ensures the radical removal of the bone tumor but at the expense of an impaired body image and compromised functional outcomes. However, amputation alone did not ensure a good survival outcome until the introduction of neoadjuvant chemotherapy and modern imaging techniques in the 1980s. With adjuvant or neoadjuvant chemotherapy for osteosarcomas, the lung metastasis rate of patients decreased and the 5-year survival rate of patients increased to 50%-80% [1-8]. Chemotherapy extends a patient's survival through decreasing the lung metastasis rate and the tumor size. Furthermore, modern imaging studies can clearly demonstrate the local extent of the tumor, thus providing a guide for wide resection with a closer surgical resection margin with the additional protection of chemotherapy.

Most malignant bone tumors of the extremity involve the major joints, i.e., the knee or hip, and therefore reconstruction of both the bone and joint is required. Some patients may have a tumor located in the diaphysis or diaphysis-metaphysis junction. Therefore many limb salvage options have been developed for treating patients with malignant bone tumors of the extremities, including resection of the tumor followed by arthrodesis of the joint, reconstruction with a bone graft (using vascularized/nonvascularized autograft reconstruction, an allograft alone, an osteochondral allograft, an allograft

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and endoprosthetic composite, or a synthetic bone graft), endoprosthetic reconstruction (utilizing total joint replacement or bone reconstruction), resection of the tumor followed by subsequent Ilizarov leg lengthening, and rotationplasty in some instances [1-17]. However, the basic requirement of any limb salvage protocol is that it needs to be safe and effective in terms of local recurrence and clinical survival.

The choice of a proper procedure needs to be made on an individual basis, by considering the radiological staging (the extent and anatomical location of the tumor, the existence of skip metastasis or lung metastasis, determination of the involvement of surrounding structures, etc.), pathological staging (histologic diagnosis, grading of the tumor, etc.), and the clinical status (patient age, local soft-tissue condition, growth potential, work requirements, lifestyle, etc.) [1-4,6,11,18]. As compared to a conventional amputation, the limb salvage procedure requires reconstruction of the defect after wide resection of the tumor. Requirements of the technique of either bone reconstruction or joint reconstruction may differ, whereas they both have to provide a tumor-free and well-functioning limb. Each choice of a limb salvage operation has its own advantages and problems, such as wound infection, soft-tissue healing, late implant failure, late leg-length discrepancy, etc. In this article, we discuss the principles of limb salvage operations and reconstruction of limb defects after wide resection.

BASIC GOALS AND RATIONALES FOR LIMB SALVAGE PRODECURES

For most malignant bone tumors involving the major joints, i.e., the knee or hip, or for tumors located in the diaphysis or diaphysis-metaphysis junction, any treatment option should offer the best expected survival rate, local control of the tumor, the best possible functions, a good body image, and psychological acceptance [2,4,8]. Limb salvage operations in well-selected patients with primary bone malignancies have demonstrated equivalent results of both survival and local control of the tumor compared to amputation [2,4, 19].

Any limb salvage operation should only be allowed when wide resection of the malignant bone tumor with an adequate margin can be assured. The basic requirements for limb salvage operations include (1) excision of the tumor with an adequate margin, (2) a local recurrence rate equivalent to or less than that with amputation, (3) the administration of adjuvant therapy as scheduled, (4) a durable reconstruction, and (5) fewer local complications [1-4,8,11]. These basic goals of a limb salvage operation should always be taken into consideration before the deciding on a choice of an operation option (Table 1).

Table 1. Basic Goals of Limb Salvage Procedure [2,6-8,11, 38,48]

(1) adequately wide resection of local tumor
(2) local recurrence rate not greater than amputation
(3) additional adjuvant therapy as scheduled
(4) enduring reconstruction
(5) low incidence of local complications

COMPARISONS AMONG VARIOUS LIMB SALVAGE PRODECURES

As mentioned above, resection arthrodesis, reconstruction with a bone graft (using an autograft or allograft), endoprosthetic reconstruction, allograft/endoprosthetic composites, Ilizarov leg lengthening, rotationplasty, etc. are the main options for managing bone tumors of the extremities [1-17]. Each limb salvage procedure has its own advantages and drawbacks (Tables 2, 3). Regardless of whether a limb salvage procedure is used to reconstruct a bone or a joint, such an operation should be decided based on individual considerations. Compared to bone reconstruction, reconstruction of a joint is more difficult because of limitations of available well-functioning structural graft material.

Resection arthrodesis refers to wide resection of a local tumor near a joint followed by an arthrodesis procedure with an autograft or allograft and implant, using either an intramedullary nail or plate fixation [1,4,9,12, 13,15]. This procedure can provide a stable, pain-free limb immediately after the operation, and the patient can return to normal daily life activities and work soon after the operation. Therefore such a procedure may be suitable for adult patients who have physically intense occupations. However, resection arthrodesis results in sacrifice of the range of motion (ROM) accompanied by a potential risk of fracture or infection. In addition, loss of ROM can limit many joint activities, such as squatting, and therefore may impair a patient's quality of life and ability to work to a certain degree.

Autografts are a common source for reconstructing a bone or joint, as well as for resection arthrodesis. Use of autografts avoids problems of tissue compatibility and immune rejection. They have better graft-host bone heal-

ing potential than other bone grafts. Autografting techniques can be used in some selected situations, for example, an iliac crest or fibula shaft for bone reconstruction after resection of some diaphyseal bone tumors. The fibular head can be used to reconstruct a distal radius tumor. However, the applicability of autografts for major joint reconstruction is limited due to scant availability. Another variant of the autograft operation uses radiation-treated specimens as the reconstruction material.

In consideration of the availability and massive structural graft, allografts are more convenient and available than autografts for reconstruction of a major joint or bone defect. However, allografts may induce immune problems, retard host-allograft bone healing, transmit bacterial and viral diseases, develop late resorption of the allograft, have a limited source of special size, have legal limitations in some countries, etc. Osteochondral allografts which can be used to reconstruct a joint have rather acceptable function [1,4,9,12-14]. However, they have the potential risks of transmission of disease, late arthritis, fracture, implant failure, and questionable growth of the allograft. Furthermore, the allograft-prosthesis composite technique is another option for joint reconstruction. This technique has the same advantages and disadvantages of allografts. It may also have prosthesis-unique complications, such as aseptic loosening, infection, etc.

Rotationplasty, i.e., wide resection of a malignant tumor followed by reconstruction using a rotated limb stump and plate fixation, can provide biological reconstruction. This procedure is usually performed in pediatric patients. For example, a defect in the distal femur can be reconstructed using the proximal femur. A defect in the proximal femur can be reconstructed using 180˚ rotation of the leg with the distal femur connecting to the acetabulum. Therefore the rotated ankle is used as the knee joint. Postoperatively, a comprehensive rehabilitation program and external prosthesis are required [10,14]. Since there are drawbacks with cosmetic problems, this procedure has been used less frequently in recent decades.

The Ilizarov leg lengthening technique is a common procedure nowadays. It can also be used for lengthening bone stumps to treat wide bone defects after wide resection of a bone tumor in some selected patients. However, this procedure requires a long time to achieve a final status of bone healing. This procedure may preserve the joint in special conditions, i.e., when the joint segment can be preserved. However, most Ilizarov leg lengthening procedures end up with arthrodesis.

Microsurgical reconstruction using a vascularized bone and soft-tissue graft may also be used to reconstruct a limb defect after wide resection of the malignant tumor [2,4,15]. It is a highly technically demanding procedure and usually takes a long time. Although bone healing may be better than that with other bone grafting techniques, the availability of a bone graft is limited due to the size and length required. Furthermore, it is time-consuming, and the potential risk of fracture is rather high because of the relatively thin dimensions.

The applicability of major joint reconstruction using an autograft, a massive osteochondral allograft, and/or an allograft-prosthesis composite is limited due to the scant source and each one's unique drawbacks. Therefore, reconstruction with a modular custom-made oncological endoprosthesis has become a common procedure nowadays. This procedure can provide a durable and functional limb immediately after the operation with a relatively low postoperative complication rate. Endoprosthetic reconstruction can avoid the potential for bacterial and viral disease, achieve immediate rigid fixation, and allow early initiation of a postoperative rehabilitation program. Therefore, increasing numbers of patients are undergoing endoprosthetic reconstruction after resection of a malignant bone tumor and some other nonmalignant conditions. However, patients' long-term survival and prosthesis survival both remain issues for patients with bone malignancies. These should be seriously considered in the future.

SPECIAL INDICATIONS AND CONTRAINDICATIONS FOR LIMB SALVAGE WITH ENDOPROSTHETIC RECONSTRUCTION

The selection of a limb salvage procedure should be carefully considered on an individual basis. An adequately wide margin of resection should always be kept in mind since no limb salvage procedure should be used at the expense of the patient's survival. Careful preoperative radiological and pathological staging studies are needed, especially in those patients undergoing endoprosthetic reconstruction. Basic imaging studies include plain radiograph, computed tomographic (CT) scan, magnetic resonance imaging (MRI) of the lesion, isotope bone scan, as well as scanograms [2,4,5,8,18, 20,21]. CT or MRI imaging studies can help demonstrate the tumor extent, possible skip metastasis or lung metastasis, and the relationship to the surrounding tissues which may suggest a more-accurate level of resection. A properly done biopsy of a bone tumor is needed to reveal the histopathological diagnosis and

grading of the tumor [2,4,5,8,18,20,21]. It is recommended that a biopsy be performed by an experienced musculoskeletal oncologist in charge to avoid biopsy-related complications.

Common indications for limb salvage of an extremity include a malignant bone tumor in the extremities with a resectable and safe margin. Different options are available for the reconstruction. Many special procedures have been designed for special situations, especially for special locations and younger patients (Tables 2, 3). Nowadays, indications for custom-made endoprosthetic reconstruction for primary malignant bone tumors of the long bones in the extremities have been expanded to other special cases, e.g., extensive metastatic lesions that cannot be reconstructed using conventional methods, isolated renal cell carcinoma metastasis, unusual or difficult multiple-recurrent or late-presenting large-stage III benign bone tumors (such as a giant cell tumor of bone), soft-tissue sarcomas with involvement of the bone, failed primary joint replacement with severe bone loss and instability, and occasional chronic recalcitrant nonunions in elderly osteoporotic patients after multiple aggressive bone grafts [2-7,10,11,16,17]. Some of the aforementioned situations may be treated with other options. Therefore, these indications for endoprosthetic reconstruction should be carefully evaluated on an individual basis.

Contraindications for limb salvage with a bone tumor of the extremities include those which cannot be resected with a safe margin, such as (1) a displaced pathologic fracture with a huge hematoma and extensive contamination; (2) an inappropriate biopsy procedure,

Table 2. Comparison among the Operation Options of Joint Reconstruction for Limb Salvage Procedures*

Procedure	Advantages	Disadvantages
Resection arthrodesis	provide a stable and pain-free limb return to work quickly	joint function sacrificed potential risk of fracture or infection impair the quality of work and life
Reconstruction with autograft	a higher healing potential feasible in selected cases	limited availability limited for the major joint reconstruction
Reconstruction with allograft, osteochondral allograft*, Allograft-prosthesis-Composite (APC)*	more convenient available for reconstruction of the major joint	slow osteosynthesis may transmit bacterial and viral disease absorbed finally limited in size and source no growth of the allograft osteochondral allograft*: late arthritis, fracture prosthesis or implant complications**
Rotationplasty	biological reconstruction	bizzare appearance need of external prosthesis comprehensive rehabilitation program
Ilizarov leg lengthening	no need of reconstruction	need a long time to achieve bone healing may need arthrodesis potential risk of infection
Microsurgery reconstruction	good bone healing good bed for soft tissue	technique demanding long time of surgery
Endoprosthesis reconstruction	provide a durable and functional limb a low post-operative complication rate avoid the potential bacterial and viral disease, achieve immediate rigid fixation and allow a early postoperation rehabilitation program	technique demanding long operation time aseptic loosening failure of implant infection wear particle disease dislodgement and dislocation insatbility of fixation

*: Common possible complications: surgery-related injuries, local tumor recurrence, eventually limb length inequality, deep wound infections and soft tissue healing problems [1-3,6-8,10,11,14-16,26,37,38,45,47,48]

i.e., one with extensive dissection and contamination across the anatomical barrier, or an improper biopsy wound site, which would make wide resection infeasible; (3) biopsy site complications, such as deep infection, a huge hematoma dissecting along the fascia plane, etc.; (4) poor soft-tissue conditions after chemotherapy or radiation therapy, such as soft-tissue or skin necrosis (a situation which might cause soft-tissue healing problems and stiffness after endoprosthetic reconstruction); (5) a large tumor encasing major neurovascular structures; (6) a poor response to adjuvant chemotherapy or radiation therapy eliminating the protective effect of adjuvant therapy on the surgical margin, (7) a very young age with great growth potential and high risk of eventual leg length discrepancy, and (8) special lifestyle and work habits, such as a heavy-duty worker who may need a stable limb with more-rigid support. The last three are relative contraindications. Similarly, these contraindications may change with the advent of additional treatment options in the future [1-7,11,16,17].

FUNCTIONAL OUTCOMES OF LIMB SALVAGE OPERATIONS

Carefully performed limb salvage operations can achieve early clinical success. Functional outcomes after any limb salvage surgery are related to the anatomical location of the tumor, the level of the resection and amount of muscle loss, the nature and amount of any preoperative adjuvant treatment protocols, the tumor size and grade, the resection operative technique, the stability of the reconstruction, the type and intensity of the postoperative rehabilitation program, and the patient's cooperation and motivation [2,4,6,19]. Preservation of an extremity certainly aids in activities of daily living, balance function, lower energy costs, cosmesis, and psychological acceptance which compare favorably with amputations and external prostheses [2-8,16,17,19].

Functional outcomes after various limb salvage procedures are difficult to compare. For example, functional outcomes of patients with diaphysis or joint reconstruc-

Table 3. Comparison among the Operation Options of Bone Reconstruction for Limb Salvage Procedures*

Procedure	Advantages	Disadvantages
Reconstruction with conventional autograft (structural or morserlized)	higher healing potential feasible in selected cases	limited availability cannot provided structural strength
Reconstruction with allograft	more convenient available for reconstruction of the major long bone	slow osteosynthesis transmit bacterial and viral disease absorbed finally potential risk of fracture implant failure limited in size and source
Ilizarov leg lengthening	no need of reconstruction easy wound closure	need a long time to achieve bone healing may end up with arthrodesis potential risk of infection technique demanding
Microsurgery reconstruction	good bone healing good bed for soft tissue	technique demanding long time of surgery risk of fracture
Intercalary reconstruction	provide a durable and functional limb a low post-operative complication rate avoid the potential bacterial and viral disease, achieve immediate rigid fixation and allow a early postoperation rehabilitation program	technique demanding long time of surgery aseptic loosening failure of implant infection wear particle disease dislodgement and dislocation insatbility of fixation

*: Common possible complications: surgery-related injuries, local tumor recurrence, eventually limb length inequality, deep wound infections and soft tissue healing problems [1-3,6-8,10,11,14-16,26,37,38,45,47,48]

tion differ. Reconstruction of the diaphysis may have a higher chance of achieving a better functional limb as compared to those who need joint reconstruction. Resection of a major joint may lead to major functional losses if the reconstruction of the joint cannot provide a well-functioning limb. In general, Enneking's functional score of these patients ranges from 70% to 90%. In addition, patients with a distal femur endoprosthesis tend to have better functional scores than those with a proximal tibial endoprosthesis. This may be related to the difficulties of soft-tissue reconstruction due to a larger segmental defect [2-7,16,17,19]. The prosthetic survival was 89% for the proximal femur, 59% for the distal femur, and 54% for the proximal tibia [7,11].

Early clinical outcomes of endoprosthetic reconstruction of an extremity are promising; however, the long-term survival of the prosthesis deteriorates year by year. Preliminary results showed that only 15%-20% of prostheses need to be revised in the early postoperative period [2,4]. Prosthesis survival is influenced by the prosthesis design, tumor site, fabrication techniques, extent of resection of soft tissue and its reconstruction, wound healing, etc. The overall general endoprosthetic survival rate was 85%-91% at 3 years, 79%-87% at 5 years, 65%-80% at 10 years, and 56% at 15 years, while 53% achieved 20-year survival [2,7,14,22,23-25]. The 10-year limb survival rate after endoprosthetic reconstruction for a distal femur osteosarcoma was 66% [2,4,7,22,25-27]. In addition, the overall revision rate for endoprostheses ranges from 15% to 45% [14,25].

COMMON PROBLEMS OF LIMB SALVAGE PROCEDURES

Taken together, surgery-related complications, e.g., neurovascular injuries, local tumor recurrence, deep wound infections, and soft-tissue healing problems, are common to all types of limb salvage procedures [1,2,4-7,16,17]. The occurrence of complications may be multifactorial, including a poor nutritional and compromised immune status due to chemotherapy, a lengthy operation, extensive dissection and resection of soft tissues, inadequate soft-tissue coverage, a longer exposure of the wound resulting in infection, etc. Early general complications include wound necrosis, infection, joint contracture, joint stiffness, joint contracture, joint instability, neuropraxia, vascular injury, etc.

Infection is one of the most-common complications of limb salvage operations. Prolonged exposure of a wound in a lengthy operation may induce deep infection. In addition, chemotherapy and/or radiotherapy, and improper oversizing of an implant may also affect the healing of the remaining soft tissue. However, deep infections in endoprosthetic reconstruction presumably occur less often than with allografts. Good soft-tissue reconstruction is needed to provide stability and adequate coverage and prevent late infectious complications. Therefore, a well-planned operation and generous utilization of muscle-flap reconstruction may avoid these problems.

Occasionally some patients may develop transient nerve palsy after proximal tibial replacement and distal femoral replacement. Most of these are transient neuropraxia which will recover later. In rare cases, patients not scheduled for resection of the involved nerve develop permanent nerve palsy. Some other patients also develop injuries to the blood vessels. On occasion, a few patients may develop deep-vein thrombosis or a thromboembolism after a limb salvage operation. Careful dissection reduces the incidences of such neurovascular complications.

Local recurrence after limb salvage indicates a failure of local tumor control. Preoperative planning must carefully make correct decisions and decrease the incidence of local recurrence. Common causes of local recurrence include the aggressiveness of the tumor with wide extension, a poor response to chemotherapy, difficulties achieving a wide safe margin, and poor local circumstances for other adjuvant therapy, such as radiation, etc. Since the local recurrence rate for limb salvage should not exceed that after primary amputation (5.8%) [2,4-7,16-18], a 4%-11% local recurrence rate after endoprosthetic reconstruction is acceptable [2,25]. To address local recurrence, some patients have a chance of reexcision of the recurrent tumor, whereas some patients may end up undergoing an amputation. Therefore, careful preoperative planning and strict selection of surgical indications with adequate wide resection and adjuvant therapy and postoperative local therapy for a possibly contaminated margin, may help reduce local recurrence. Furthermore, close regular follow-up is indicated for high-risk patients for the early detection and treatment of local recurrence.

In addition, no limb salvage alternatives can avoid the problems of eventual limb length inequality in skeletally immature patients. This is caused by the impaired growth potential after removal of a major growth plate. The resultant leg length discrepancy may compromise the function and cosmetic appearance in pediatric patients. In addition to unequal limb length, a patient may develop a varus or valgus deformity, inappropriate proportion of a limb segment, and eventual inevitable loss of height [2,4,5,7,28,29]. The development of an

expandable prosthesis provides a possible solution at the expense of a higher rate of complications and multiple lengthening revisions, either by a revision operation, by an external magnetic field, or by knee-bending kinetic energy [2,7,20,28-32]. The risk of infection and a high incidence of other complications merit further investigations.

ENDOPROSTHESIS-RELATED COMPLICATIONS

The use of a relatively smaller stem in pediatric patients, a higher activity level, little soft-tissue support for stability of fixation, a larger exposed surface, and higher mechanical stress may contribute to higher rates of early or late complications after endoprosthetic reconstruction than for those undergoing conventional joint arthroplasty. Complications include wound necrosis, deep-wound infections, joint instability, subluxation or dislocation, joint contracture or stiffness, malalignment of the patella, fatigue fracture, prosthetic loosening, polyethylene wear, leg length discrepancy, local recurrence, and soft-tissue healing problems [2,4,7,29,30,33]. Disease due to wear particles occurs frequently in patients undergoing custom-made endoprosthetic reconstruction and leads to osteolysis and loosening. Overall complication rates were 20%-41%, including infection (5%-15%), local recurrence (4%-11%), mechanical failure (5%-16%), dislocation or instability (5%-8%), prosthetic failure (5%), loosening (2%-7%), polyethylene wear (2%), wound complication (6%), and neuropraxia (5%) [2,8,14,22,26,27,29,34-36]. Expandable prostheses have even higher complication rates of up to 70% [2,7,25,28-32,37].

Complications may affect the function and quality of life of patents. To address these complications, careful repair of the soft tissue and joint capsule, selection of a proper design and size, as well as appropriate protection in the initial postoperative period may be helpful. Many prosthesis-related complications are frequently caused by local stress concentrating on the prosthesis itself or to the prosthesis-bone interface. We also need to improve the design, material, and fixation [4-7,16, 17], such as maximizing the diameter of the intramedullary stems. In addition, early detection and early correction of minor complications can reduce the risk of implant failure and eventual disaster, such as revision or at times, amputation [2,4-7,35].

SUMMARY

The prognosis of patients undergoing limb salvage surgery is multifactorial, including the character of the tumor (its anatomical location, size, grade, soft-tissue involvement, etc.). Careful preoperative planning may determine the possibility of wide resection and proper reconstruction. Therefore, during selection of a limb salvage modality, one needs to carefully consider the radiological staging, pathological staging, and clinical status. Amputation should be considered when patients display any contraindications for limb salvage. The level of resection of the tumor, the amount of muscle loss, and reconstruction options may all influence the functional outcome. Different types of resection techniques may produce different results. For example, extra-articular resection of the distal femur or proximal tibial tumor may cause greater loss of the surrounding tissue. The results may be worse compared to those patients undergoing intra-articular tumor resection. Resection arthrodesis may be indicated for a durable limb with rigid support but at the expense of joint function.

The basic design of an endoprosthesis, soft-tissue healing, the stability of reconstruction, and the range of motion of the prosthesis may all influence the functional outcome. Furthermore, preoperative adjuvant treatment, the type and intensity of postoperative rehabilitation program, and the patient's level of cooperation and motivation are all prognostic factors. At present, selection of a proper limb salvage option and a skillful surgical technique in addition to an immediate comprehensive rehabilitation program may maximize the chances of achieving a well-functioning limb. However, we need to pay attention to regular follow-up and late complications in patients with longer survival times after chemotherapy.

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