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Original article

Megaprosthesis of the knee in tumor and revision surgery

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Summary. The introduction of multidisciplinary approach with chemo and radiotherapy, the advances in surgical and the improvements of diagnostic techniques allowed limb salvage surgery in most cases of bone sarcomas instead of amputation. Modular megaprostheses are the most common method of reconstruction after segmental resection of the long bones in the extremities for their availability, immediate fixation, early weight bearing, good function. Despite the advances in materials and implant designs, these systems have an high incidence of complications. Aim of this study was to report the experience on mega-prostheses implanted around the knee in tumor and revision surgery to analyze: the most frequent used current systems, the problems of stems fixation, extensor mechanism reconstructions in proximal tibia resections and the preservation of growth of the lower extremity in children. (www.actabiomedica.it)

Key words: UKA, medial, lateral unicompartmental artrhroplasty, unicondylar

Background and aim of the work

The introduction of multidisciplinary approach with chemo and radiotherapy, the advances in surgical and the improvements of diagnostic techniques allowed limb salvage surgery in most cases of bone sarcomas instead of amputation (1-10).

Reconstruction techniques following limb salvage include massive allografts or allograft-prosthetic composites, endoprostheses, rotationplasty and arthrodesis (10-13).

Modular megaprostheses have been used more frequently in the last three decades and are now the most common method of reconstruction after segmental resection of the long bones in the extremities for their availability, relative ease use, immediate fixation, early weight bearing, relatively rapid restoration of function and excellent cosmetic appearance (1, 6, 9, 14).

Despite the advances in materials and implant designs occurred over the years, these systems have an incidence of complications and failures higher than conventional implants, making revision surgery relatively frequent (1, 7, 9, 10, 14-26). Many factors are related to the high incidence of complications such as immunosuppression due to chmotherapy, extensive bone and soft tissues resections, longer operative time and general patient condition.

Aim of this study was to report the experience on mega-prostheses implanted around the knee in tumor and revision surgery to analyze: the most frequent used current systems, the methods of stems fixation, the types and incidence of failures, the problem of extensor mechanism reconstructions and the growth of the lower extremity in children.

Types of prostheses

Several types of megaprostheses implants are currently available for limb salvage surgery and the follow are the most frequently used: the GMRS®, the Mutars®, the Compress®, the Stanmore®, Exactech® (7, 10, 14-16, 27-33).

The Kotz Modular Femur-Tibia Reconstruction system (KMFTR®, Howmedica Modular Reconstruction System, Stryker, UK) was one of the first modular fixed-hinge knee system, introduced in 1982 (23, 27-29).

The diaphyseal anchorage of the system was provided by an intramedullary stem with two lateral flanges with three holes for totally six screws through the stem and the cortex (23). Most of these implants had a progressive wear of the polyethylene bushings with subsequent loosening and the nearest hole for cross screw fixation was the most frequent site of stem breakage (29, 34-36).

Mittermayer et al. (23) reported the long-term results of 100 patients: the most common reason for failure in their series was aseptic loosening in 27% of patients.

In 1988, the design of KMFTR® was revised in the fixed-hinge Howmedica Modular Reconstruction System (HMRS®, Howmedica Modular Reconstruction System, Stryker, UK); it incorporates an anatomical femoral stem with one lateral flange (to reduce the stress-shielding effect), a new hinge design and a new generation polyethylene (10, 27-29, 34, 35, 37).

Both these fixed-hinged knee prostheses were associated with abnormal kinematics and excessive stress to the prosthesis and bone interface (29-31, 38).

We reviewed the results on 669 patients treated with resection and reconstruction using modular fixed-hinge KMFTR® and HMRS® megaprostheses between 1983 and 2006 (27).

Overall 4.8% prostheses broke and required revision; breakage occurred in 10.5% KMFTR® prostheses and in 3.5% HMRS® prostheses with a statistically significantly higher survival to breakage was for the HMRS® prostheses (p=0.008) (27).

Aseptic loosening was lower in HMRS® prostheses (4.9%) than in KMFTR® (9.6%) but a difference in survival to this complication between the two types of implants was not observed (p=0.654).

In our experience, even if with we know the risk of this complications, the HMRS® prostheses is still indicated for knee stability in patients with extensive quadriceps muscle excision (39), total femoral reconstructions, and probably elderly, debilitated and with minor muscle strength patients.

The rotating-hinge Global Modular Reconstruction System (GMRS) was the evolution of the previous HMRS® and has been available since 2003; the addition of a rotating hinge was a significant design modification that help to reduce mechanical stresses and complications at the bone implant interface (1, 27, 40).

We reviewed our experience with 295 GMRS prostheses implanted between 2003 and 2010 (1); no cases of breakage of prosthetic components or peri-prosthetic fractures were observed with this prostheses (40).

Aseptic loosening, even if lower than in fixed-hinge knee series, remains a common cause of implant failure also in the current generation of implants (1, 40).

In our series on 295 GMRS prostheses implanted in the lower limb the incidence of aseptic loosening was 5% (40). When we analyzed the results with 247 GMRS prostheses implanted around the knee, we found a 5% incidence of aseptic loosening (1).

The functional results were good with a mean score of 24.5/30 according to the Tumor Society score (40).

Compressive osteointegration technology is a novel approach to reduce the high rates of osteolysis after proximal tibial and distal femoral reconstructions (30, 31, 41, 42).

Dynamic compression fixation (Compress) of tumor prostheses aim to achieve biomechanical stable and durable implants while stimulating osseointegration and improve the long term survivorship of the implant through active osseointegration (30, 31, 41-44).

This technology was applied in the Compress Pre-Stress Implant (Biomet Inc, Warsaw, IN).

This implant utilizes spring tension with short traction bar to achieve high compressive forces at the bone-prosthesis interface, promote hypertrophy of the loaded bone, and avoid stress bypass of the host bone around a stiff intramedullary stem; these implants aim to provide stabilization without the need for long-stem fixation with the benefits of decreased stress shielding, diminished particle-induced osteolysis, and increased osteointegration at the bone implant interface (44-46).

A common complication of this implant is aseptic loosening that is different from that seen with other implants since bone ingrowth failed despite the continuously adjusting compression generated by the Belleville washers in the compression chamber (44).

A second, related unique finding was fracture or crumbling of the underlying bone between the anchor plug and the spindle.

Healey et al. (44) reported 9.7% (8/82 patients) incidence of failures of the interface due to aseptic loosening or aseptic loosening associated with periprosthetic fractures that affected the interface. De-

spite the complications, Healey et al. (44) reported a survivorship of the Compress® fixation of 85% at 5 years and 80% at 10 years.

The Stanmore prosthesis has the longest clinical history and was first implanted in 1949, it is a custom made prosthesis, initially with cemented fixation but since 1991 a cementless version has been available with a hydroxyapatite-coated titanium stem (47-49).

The shaft and intramedullary stem were made from titanium alloy (Ti 318 [Ti-6Al-4V]); the hinge of the knee joint is rotating (Stanmore Modular Individualised Lower Extremity System, SMILES) made from cast cobalt-chromium-molybdenum alloy (50).

Unwin et al. (48) reviewed 1001 patients treated since 1993; in this series the principal cause for failure was aseptic loosening with a rate of 9.9% in the distal femur, 6.5% in the proximal tibia and 2.3% in the proximal femur.

Coathup et al. (50) analyzed the results of 61 reconstructions with a cemented distal femoral endoprosthesis with a hydroxyapatite coated collar performed at the Royal National Orthopaedic Hospital (RNOH) in Stanmore. They demonstrated that at the ten-year follow-up interval, 66% of patients had an osteointegrated collar and a radiographic evidence of osteointegration of the collar was observed in 70% of patients over a two to eighteen-year follow-up period. Their study showed a low rate of revision due to aseptic loosening (8%) with a survival rates to aseptic loosening in their series was 93.7%, 88.9%, at five, ten ten years, respectively (50).

MUTARS® system (Modular Universal Tumour And Revision System, Implantcast, Buxtehude, Germany) was introduced in 1995. The intramedullary stem is curved to follow the anterior bow of the medullary cavity of the femur and can be inserted press-fit or cemented. The stem has an hexagonal cross section and is made of titanium alloy (TiAl6V4) in the cementless version and of CoCrMo alloy in the cemented version (19, 49). The hexagonal-shaped design of the stem should provide good rotational stability reducing loosening rates and less stem breakage (7).

Gosheger et al. (7) reported the results in 250 cases of Mutars prostheses replacement; they reported and incidence of complication in line with the literature: 12% of deep infection, 8% aseptic loosening and 1.6% stem fracture; the MSTS functional results were good and ranged between 63% to 83% according to the Tumor Society score (7).

Heisel et al. (49) reported their experience in more than 100 cases of MUTARS system; in their series the main complication were aseptic loosening (22%) and deep infections (12%). They looked at different variables influencing the incidence of aseptic loosening, but all showed no significant influence. No fractures around the bone-prosthesis junction occurred (49).

Stem fixation: cemented or press-fit

The mode of stem fixation, cemented vs uncemented, is of remarkable importance. Cemented stems have been reported in most of the literature as having an higher rate of aseptic loosening (13, 23, 25, 26, 41, 51).

In literature there is no clear support regarding one method of fixation vs another and it remains unclear whether cementless tumor prostheses have comparable survival and complications with cemented prostheses (13,14,23,26,41,52).

Cementless fixation may be advantageous because of bone in-growth surface that may lead to a low aseptic loosening rate (13,36).

Press-fi t stems have been constructed of varied shapes (eg, fluted, fenestrated) and textures (eg, grit-blasted, porous-coated, beaded) with the aim of obtain osteointegration into the surrounding bone (41).The introduction of hydroxyapatite (HA) and HA-tricalcium phosphate stem coatings potentiates osteogenic adhesion to metallic surfaces and has positively impacted tumor endoprosthesis fixation and survival (41).

When utilizing uncemented stems, provisional rotational stability needs to be addressed in order to provide initial constraint and allow for osseous ingrowth (36,41,53).

Current systems utilize various methods to reduce rotational stresses, including anti-rotational fins, hexagonally shaped stems, fixation plates, and spring tension to achieve high compressive forces (7,17,19,23,30,31,42,46)

We retrospectively studied 232 patients treated with modular prostheses between 2002 and 2007; cemented stem fixation was done in 124 (53.4%) cases and cementless in 108 (46.6%) cases (13).

In this series the overall survival and survival to infection is higher for cementless than cemented stem fixation but survival to aseptic loosening is not different between the two types of stems fixation (13).

We recommended cemented fixation in patients with bone metastases, extensive osteolytic defects such as hemoproliferative lesions, patients with a poor prognosis, and older patients to be bear full weight immediately. In younger patients and in primary bone tumors we recommended cementless fixation (13).

Types of failures

Despite the advances in materials and implant designs occurred over the years, these systems have an incidence of complications and failures higher than conventional implants, making revision surgery relatively frequent (1,7,9,10,14-26).

In 2011 Henderson et al. (20) published the new classification of failure in megaprosthesis; this classification included five types of failure: soft tissues failure (Type 1), aseptic loosening (Type 2), structural fracture (Type 3), infection (Type 4), and local tumor recurrence (Type 5).

Soft-tissue failures are defined as functional deficiencies of the soft-tissue attachments about the implant that require re-operation (20,41) These failures may be due to disruption or incompetence of periarticular ligamentous and tendinous restraints that lead to instability or failure of incorporation or ingrowth of host tendons to the endoprosthesis. In the multicentric study reported by Henderson et al. (20), soft-tissue failures accounted for 12% of all failures, with an absolute incidence of 2.9%. It was most common around the shoulder and hip, where soft tissue is critical for joint function and stability.

Aseptic loosening remains a major problem after prosthetic replacement of large bone defects; in the literature the incidence range between 4.9% and 9.6% (1, 14, 23, 25, 27, 42, 51, 52).

The incidence depends on the reconstruction site, with the highest rates of loosening in distal femoral replacement (7,23).

The shape of the distal femur stem is important; anatomically curved femoral stems are reported to achieve a long press-fit stem anchorage (7, 10, 23).

Gosheger et al. (7) suggest preparing the medullary cavity with a hexagonal rasp and implanting the HA-coated titanium stem led to good primary rotation stability and excellent secondary osseointegration.

In contrast to constrained prostheses, using the rotating-hinge mechanism for the knee prostheses, rotational stress is resorbed mainly by the joint instead of the stem, reducing the risk of aseptic loosening (1, 7, 23, 54).

In the meta analysis of the literature published by Henderson et al. (20), the rate of breakage of the prosthetic component (Type 3 failure) in distal femur reconstruction was 6.3%, whereas in the proximal tibia, the range in the literature was between 2% and 12% (7,14,17,42). In our series of megaprostheses around the knee, breakage of the prosthetic component did never occurred (1).

Infection

Complex arthroplasty and reconstruction procedures, large implant sizes, greater surgical exposure, extensive resection of bone and soft tissues, lack of soft tissue cover, long operating times, immunosuppression caused by chemotherapy, radiotherapy and anemia are the major factors related with higher infection rates of tumor prostheses compared with conventional arthroplasties performed for arthritis (10, 14, 21, 22, 31, 42, 55, 56, 57). In the literature, infection has been reported to be the most common mode of failure in megaprostheses, ranging between 5% and 40% (7, 14, 18, 20, 21, 22, 40). The risk of secondary amputation due to the persistent of infection is between 23.5% and 87% (17,21,37,51,55,61).

Staphylococci are the most common pathogens involved in prosthetic joint infections (approximately 50% of infections overall), followed by streptococci, enterococci, Enterobacteriaceae species, Pseudomonas aeruginosa, and anaerobe species (21,55).

Multiple pathogens may be isolated in approximately 25% of cases, with the most common combination of coagulase-negative Staphylococcus and group-D Streptococcus (21).

Prosthetic joint infections have been classified as: post-operative (occurring within 4 weeks after the operation), early (occurring between 4 weeks and 2 years

after the operation), late (occurring after two years) (55).

One-stage revision included debridement of the joint, change of modular components, retaining the prosthetic stem, prolonged antibiotic therapy (58,59). One-stage revision has been recommended for patients with early or low-grade infections, caused by low-virulence microorganisms, patients with a short duration of symptoms and early diagnosed infection and high antibiotic-sensitive pathogens, well-fixed implants, poor general condition of the patient, and long delay of chemotherapy (18,22,55).

Two-stage revision of infected tumor prostheses included the complete removal of all prosthetic components (including the stems), antibiotic-loaded cement spacer and long timeuse of systemic antibiotics (55,58). Two-stage revision is recommended for patients with persistent, higher-grade infections, extensive osteolysis with megaprosthesis loosening and bone loss, poor soft tissue envelope, antibiotic-resistant pathogens, and a failed one-stage procedure (55,60). After a long period of administration of systemic antibiotics (up to 6 weeks postoperatively), a second stage surgery for reimplantation of a new prosthesis, 2 or more months later is performed (55,61).

From 1983 to 2010, 1161 patients underwent megaprosthesis reconstruction at the authors' institution after limb salvage surgery for a sarcoma; among these, 100 patients (8.6%) had infection at a mean time of 3.7 years. The most common microbial isolate was Staphylococcus epidermidis followed by S. aureus, Pseudomonas spp and multiple isolates (61).

The overall prevalence of infection was higher for late (6.3%) than for early (1.4%) and acute (0.9%) infections. Proximal tibia megaprosthesis reconstructions are the most common site of infection (27 of 226; 11.9%) than other sites (61).

Most cases were treated with Two-stage revision (83 cases), one-stage revision was performed only in 12 cases, and amputation as first treatment in 5 cases (61).

Resolution of infection was provided in 75% of infections, however, amputation was necessary as the first treatment or after persistence or recurrence of the infection in 21% of the patients with infected megaprostheses. The survival rate is higher for cementless megaprosthesis reconstructions and no different with respect to the type of the tumor, type of megaprosthesis, and administration of adjuvant treatments (61).

The severe consequences of infection underline the importance of prevention infection. For this reason, several methods have been devised to decrease the risk of contamination and colonization of the implant; these included hygienic precautions, the development of hydrophilic materials to minimize bacterial adhesion, and impregnation with antiseptics and antibiotics.

Among metals with antimicrobial activity, silver has raised the interest of many investigators because of its good antimicrobial action and low toxicity (62).

Silver compounds are poorly water soluble, resulting in low concentrations of silver ions released into the surrounding tissue and blood, therefore local or systemic side-effects were not observed (62,55,56).

Silver-coated megaprostheses have been introduced in musculoskeletal oncology surgery considering the higher rate of infection than standard implants (63,64).

In Mutars megaprostheses silver coating was applied to the titanium–vanadium by galvanic deposition of elementary silver (with a percentage purity of 99.7%) onto the surface of the prostheses. Additionally, a layer of gold 0.2 mm thick between the titanium–vanadium surface of the prosthesis and the silver coating was designed to allow sustained release of silver ions into the periprosthetic tissue. No silver coating was applied at the articulating surfaces or prosthetic stems (57).

Schmolders et al. (64) analyzed the results in 100 patients treated with a silver-coated tumor megaprosthesis; they concluded that megaprosthetic joint infection in silver-coated implants is lower compared to non-silver-coated implants.

Donati F. et al (63) retrospectivly reviewed 68 proximal femur reconstructions with modular prostheses comparing silver-coated MUTARS hip hemiarthroplasty (55.9% of cases) with uncoated titan MUTARS modular tumor hip prosthesis (44.1% cases). This study confirmed the protective role of silver coating compared with standard titan megaprosthesis, especially in the first 6 months after surgery; they observed that the silver coating has partially lost his full

effect by the time, due to his physiological mechanical erosion; it could explain why infection risk between silver-coated prostheses and titan one is comparable for late infection (63). Furthermore no significant local or general signs of toxicity secondary to silver ions exposition were reported (63).

However the economic factor has to be considered; silver coated megaprostheses are 5–7% more expensive than the other tumor prostheses but considering considering the decrease in the period of hospitalization and in revision surgeries for infection it could be a good choice of implant (62,63).

The problem of extensor mechanism reconstruction in proximal tibia

Proximal tibial megaprosthetic reconstructions have been related with the least favorable outcome and highest rate of complications of all limb salvage procedures (65-68).

The problems in proximal tibia reconstructions are related to the relative lack of wound coverage and unreliable options for extensor mechanism reconstruction. The medial gastrocnemius flap is the best choice for both reconstruction of the extensor mechanism and adequate coverage of the prostheses, which likely reduces the infection rate (1,65,66).

Many studies reported various techniques for attachment of the extensor mechanism of the knee and coverage of proximal tibia reconstructions such as direct fixation of the extensor mechanism to the megaprosthesis using screws, sutures, loops and mechanical clamping, biological augmentation using hydroxyapatite coating of the megaprosthesis, or autologous bone grafting at the tendon–implant interface, artificial ligaments and synthetic materials such

as polyethylene, fibula transposition, pedicled muscle flaps, and combined techniques (66-75).

The direct attachment of the extensor mechanism to the megaprosthesis is important to provide the initial mechanical stability needed for healing and scarring (65,67,68,71-75).

Artificial ligaments and synthetic materials often result in synovitis, infection, and loosening or stretching of the patellar tendon (72). Pedicled medial or lateral gastrocnemius muscle flaps have been used to provide the necessary blood supply for wound healing and biological reconstruction of the extensor mechanism, and reduce the risk of infection (65, 67, 68, 70, 72, 75).

We reported the results of 225 proximal tibial resection and megaprosthetic and extensor mechanism reconstruction between 1985 and 2010 (66). In most of the cases (167/225) the extensor mechanism was attached to a gastrocnemius muscle flap and approximated to the megaprosthesis without tension using non-absorbable sutures inserted through the anterior holes of the prosthesis. Direct attachment of the patellar tendon to the megaprosthesis with medial gastrocnemius muscle flap, with or without artificial ligament, was related with the less extension lag. We recommend the use of the gastrocnemius muscle flap for augmentation of the extensor mechanism and wound coverage, and augment the extensor mechanism reconstruction with synthetic materials or artificial ligament in patients with atrophic gastrocnemius muscle because of inactivity, increased age, chemotherapy, or radiation therapy (66).

Expandable tumor prostheses in children

Primary bone tumors in children are frequently found close to the physes of long bones, most commonly around the knee. The epiphyses of the distal femur and proximal tibia contribute approximately 35% and 30%, respectively, to growth of the lower extremity (32, 33, 76-78).

Any surgical resection in this age will cause a limb-length discrepancy from continued growth of the contralateral lower extremity resulting in gait disturbances, low back pain, and cosmetic effects on the shortened leg (32, 33, 78).

Complete tumor resection, avoidance of the limb length discrepancy, and good functional outcome are the main goals of tumor surgery in children.

We present 32 children with bone sarcomas of the femur treated with limb salvage and reconstruction using three types of expandable prostheses between 1996 and 2010. We used the minimally invasive open procedure lengthening Kotz Growing prosthesis (KM-FTR; Howmedica Modular Reconstruction System, Stryker, UK) in 10 children; the Repiphysis (Wright Medical Technologies, Arlington, TN) or Phenix

Prosthesis (Phenix Medical, Paris, France) was used in 15 children; the Stanmore custom-made prosthesis (Extendable Mark V, Stanmore Implants Worldwide, Stanmore, Middlesex, England, UK) was used in 7 children (33).

The first models required open lengthening procedures, with the patient under anesthesia, and lengthening was performed by introducing a spacer Open lengthening procedures for the invasive lengthening were accompanied by the risk of ankylosis, nerve damage, and infection (79, 80).

The noninvasive lengthening expandable prostheses such as the Repiphysis or Phenix Prosthesis and the Stanmore prosthesis were designed for using an external electromagnetic or rotating magnetic field, aiming to minimize the risk of complications because of open lengthening procedures (32, 33, 81-83).

In the Stanmore prostheses the expansion is achieved by electric current that produces a rotating magnetic field, which is captured by a magnet within the implant and extends a gearbox (32, 33, 48, 82).

Aseptic loosening has been the common mode of failure of expandable prostheses due to circumferential or appositional bone growth that results in widening of the bone and the intramedullary canal with consequent loosening of the prosthesis (32, 33, 48, 76, 78, 81, 82).

Neurovascular compromise is minimal if lengthening is <20 mm (81).

To avoid joint stiffness, small lengthening of 6 to 10mm per procedure, rehabilitation to address flexion contractures, have been recommended (84).

In our series the survival of the Repiphysis prostheses was 32% at 72 months thereafter, all Repiphysis prostheses failed. The survival of the Stanmore prostheses was 100% at 48 months. The difference in survival to failure between the 3 types of primary expandable prostheses was statistically significant (log-rank test, P=0.030) with better survival for Stanmore prostheses (33).

The mean total lengthening of the expandable prostheses was 28mm that was achieved by a total of 84 planned procedures. Nine of the 26 children who were still alive reached skeletal maturity; 3 of these children had limb-length equality and 6 had limb-length discrepancy of 15 to 30 mm.

In children with noninvasive prostheses, we opted for small lengthenings of 4 to 10 mm at each follow-up examination. On the tibial side, we use of a smooth non cemented intramedullary stem placed through the center of the physis to anchor the prosthesis without bone ingrowth that might interfere with the growth plate and create further limb shortening or angular deformity of the tibia. Because of the cost and high rate of implant-related complications, we do not use expandable prostheses in children with expected growth remaining <2 cm and adolescents. In these cases, we are in favor of the standard adult-type megaprosthetic reconstructions, with or without contralateral epiphysiodesis, as necessary, with excellent results (33).

Conclusions

With regard to the published studies, the support of one specific system is not possible. Surgeons should choose systems with which they are familiar and provide the modular options needed intraoperatively to bridge any defects of the lower limb. The addition of the rotating hinge for the knee was a significant design modification that help to reduce mechanical stresses at the bone implant interface that can cause loosening or fractures. In literature there is no clear support regarding one method of stem fixation (cemented vs press-fit) but cementless fixation seems to improve the bone in-growth that may lead to a low aseptic loosening rate. Despite the advances in materials and implant designs, these systems have an high incidence of complications and infection has been reported to be the most common mode of failure in megaprostheses. Some studies confirmed the protective role of silver coating implants with no significant local or general signs of toxicity secondary to silver ions exposition. In proximal tibia reconstructions we recommend the use of the gastrocnemius muscle flap for augmentation of the extensor mechanism for wound coverage and reduce the risk of infection. In children the noninvasive lengthening expandable prostheses are the key to avoid leg length discrepancy of the lower extremity. Multicentric cooperative studies are the key to further progress.

Conflict of Interest Statement: Pietro Ruggieri is consultant designer for Stryker and Exactech. Other authors certified that they have no commercial association that might pose a conflict of interest in connection with the submitted article

References

1. Pala E, Trovarelli G, Calabrò T, Angelini A, Abati CN, Ruggieri P. Survival of Modern Knee Tumor Megaprostheses: Failures, Functional Results, and a Comparative Statistical Analysis. Clin Orthop Relat Res 2014 May 30,
2. Bacci G, Ferrari S, Bertoni F, Ruggieri P, Picci P, Longhi A, Casadei R, Fabbri N, Forni C, Versari M, Campanacci M. Longterm outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the Istituto Ortopedico Rizzoli according to the Istituto Ortopedico Rizzoli/osteosarcoma-2 protocol: an updated report. J Clin Oncol 2000; 18: 4016-27.
3. Bacci G, Ferrari S, Comandone A, Zanone A, Ruggieri P, Longhi A, Bertoni F, Forni C, Versari M, Rimondini S. Neoadjuvant chemotherapy for Ewing's sarcoma of bone in patients older than thirty-nine years. Acta Oncol 2000; 39: 111-6.
4. Campanacci M. Bone and Soft Tissue Tumors. New York, NY, USA: Springer-Verlag; 1999: 1-70.
5. Eckardt JJ, Eilber FR, Dorey FJ, Mirra JM. The UCLA experience in limb salvage surgery for malignant tumours. Orthopedics 1985; 8: 612-21.
6. Mirra JM, Picci P, Gold RH, eds. Bone Tumors: Clinical, Radiologic and Pathologic Correlations. Vol. 1. Philadelphia, PA, USA: Lea & Febiger; 1989: 248-62.
7. Gosheger G, Gebert C, Ahrens H, Streitbuerger A, Winkelmann W, Hardes J. Endoprosthetic reconstruction in 250 patients with sarcoma. Clin Orthop Relat Res 2006; 450: 164-71.
8. Rougraff BT, Simon MA, Kneisl JS, Greenberg DB, Mankin HJ. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur: a long-term oncological, functional and quality of life study. J Bone Joint Surg Am 1994; 76: 649–656.
9. Ruggieri P, Bosco G, Pala E, Errani C, Mercuri M. Local recurrence, survival and function after total femur resection and megaprosthetic reconstruction for bone sarcomas. Clin Orthop Relat Res 2010; 468: 2860-6.
10. Zeegen EN, Aponte-Tinao LA, Hornicek FJ, Gebhardt MC, Mankin HJ. Survivor analysis of 141 modular metallic endoprostheses at early followup. Clin Orthop Relat Res 2004; 420: 239-50.
11. Gebhardt MC, Flugstad DI, Springfield DS, Mankin HJ. The use of bone allografts for limb salvage in highgrade extremity osteosarcoma. Clin Orthop Relat Res 1991; 270: 181-96.
12. Mankin HJ, Gebhardt MC, Jennings LC et al. Long term results of allograft replacement in the management of bone tumors. Clin Orthop Relat Res 1996; 324: 86-97.
13. Pala E, Mavrogenis AF, Angelini A, Hendreson ER, Letson DG, Ruggieri P. Cemented versus cementless endoprostheses for lower limb salvage surgery. J BUON 2013 Apr-Jun; 18(2): 496-503.
14. Ahlmann ER, Menendez LR, Kermani C, Gotha H. Survivorship and clinical outcome of modular endoprosthetic reconstruction for neoplastic disease of the lower limb. J Bone Joint Surg Br 2006; 88: 790-5.
15. Bhangu AA, Kramer MJ, Grimer RJ, O'Donnell RJ. Early distal femoral endoprosthetic survival: cemented stems versus the compress implant. Int Orthop 2006; 30: 465-472.
16. Biau D, Faure F, Katsahian S, Jeanrot C, Tomeno B, Anract P. Survival of total knee replacement with a megaprosthesis after bone tumor resection. J Bone Joint Surg Am 2006; 88: 1285-93.
17. Grimer RJ, Belthur M, Chandrasekar C, Carter SR, Tillman RM. Two-stage revision for infected endoprostheses used in tumor surgery. Clin Orthop Relat Res 2002; 395: 193-203.
18. Hardes J, Gebert C, Schwappach A, Ahrens H, Streitburger A, Winkelmann W, Gosheger G. Characteristics and outcome of infections associated with tumor endoprostheses. Arch Orthop Trauma Surg 2006; 126: 289-96.
19. Heisel C, Breusch SJ, Schmid G, Bernd L. Lower limb salvage surgery with MUTARS endoprostheses: 2 to 7 year results. Acta Orthop Belg 2004; 70: 142-7.
20. Henderson ER, Groundland JS, Pala E, Dennis JA, Wooten R, Cheong D, Windhager R, Kotz RI, Mercuri M, Funovics PT, Hornicek FJ, Temple HT, Ruggieri P, Letson GD. Failure mode classification for tumor endoprostheses: retrospective review of five institutions and a literature review."J Bone Joint Surg Am 2011 Mar 2; 93(5): 418-29. Review.
21. Jeys LM, Grimer RJ, Carter SR, Tillman RM. Periprosthetic infection in patients treated for an oncological orthopaedic condition. J Bone Joint Surg Am 2005; 87: 842-9.
22. Lee SH, Oh JH, Lee KS, Yoo KH, Kim HS. Infection after prosthetic reconstruction in limb salvage surgery. Int Orthop 2002; 26: 179-84.
23. Mittermayer F, Windhager R, Dominkus M, et al. Revision of the Kotz type of tumour endoprosthesis for the lower limb. J Bone Joint Surg Br 2002; 84(3): 401-6.
24. Natarajan MV, Sivaseelam A, Ayyappan S, Bose JC, Sampath Kumar M. Distal femoral tumours treated by resection and custom mega-prosthetic replacement. Int Orthop 2005; 29: 309-13.
25. Sharma S, Turcotte RE, Isler MH, Wong C. Experience with cemented large segment endoprostheses for tumors. Clin Orthop Relat Res 2007; 459: 54-9.
26. Turcotte RE. Endoprosthetic replacements for bone tumors: review of the most recent literature. Curr Opin Orthop 2007; 18: 572-8.
27. Ruggieri P, Mavogenis AF, Pala E, Magdy AM, Mercuri M. Long Term Results of fixed-hinge megaprostheses in limb salvage for malignancy. The knee 2012; 19(5): 543-9.
28. Kotz R, Ritschl P, Trachtenbrodt J. A modular femur-tibia reconstruction system. Orthopedics 1986; 9: 1639-52.

29. Kotz R. The development of a modular tumor endoprosthesis (KMFTR-HMRS-GMRS). Evolution, results and perspectives. Archivio di Ortop e Reumatol 2005; 116(2): 9-11.
30. Myers GJC, Abudu AT, Carter SR, Tillman RM, Grimer RJ. Endoprosthetic replacement of the distal femur for bone tumors. Long term results. J Bone Joint Surg 2007; 89B: 521-6.
31. Myers GJC, Abudu AT, Carter SR, Tillman RM, Grimer RJ. The long-term results of endoprosthetic replacement of the proximal tibia for bone tumors. J Bone Joint Surg 2007; 89B: 1632–7.
32. Mavrogenis AF, Papagelopoulos PJ, Coll-Mesa L, Pala E, Colangeli M, Manfrini M, Ruggieri P. Expandable tumor prostheses in children. J BUON 2012 Jan-Mar; 17(1): 9-15.
33. Ruggieri P, Mavrogenis AF, Pala E, Romantini M, Manfrini M, Mercuri M. Outcome of Expandable Prostheses in Children. J Pediatr Orthop 2013 Apr-May; 33(3): 244-53.
34. Campanacci M, Capanna R, Ruggieri P, Ritschl P, De Cristofaro R, Ferraro A, et al. Cementless modular prosthesis. Results and complications. Chir Organi Mov 1990; 75(Suppl 1): 179-83.
35. Lan F, Wunder JS, Griffin AM, Davis AM, Bell RS, White LM, et al. Periprosthetic bone remodelling around a prosthesis for distal femoral tumors. Measurement by dual-energy X-ray absoptiometry (DEXA). J Bone Joint Surg 2000; 82-B: 120-5.
36. Griffin AM, Parsons J, Davis AM, Bell RS, Wunder JS. Uncemented tumor endoprostheses at the knee: root causes of failure. Clin Orthop Relat Res 2005; 438: 71-9.
37. Ilyas I, Kurar A, Moreau PG, Younge DA. Modular megaprosthesis for distal femoral tumors. Int Orthop 2001; 25: 375-7.
38. Kabo JM, Yang R, Dorey FJ, Eckardt JJ. In vivo rotational stability of the kinematic rotating hinge knee prosthesis. Clin Orthop Relat Res 1997; 336: 166-76.
39. Capanna R, Ruggieri P, Biagini R, Ferraro A, DeCristofaro R, McDonald D, et al. The effect of quadriceps excision on functional results after distal femoral resection and prosthetic replacement of bone tumors. Clin Orthop Relat Res 1991; 267: 186-96.
40. Pala E, Henderson ER, Calabrò T, Angelini A, Abati CN, Trovarelli G, Ruggieri P. Survival of current production tumor endoprostheses: Complications, functional results, and a comparative statistical analysis. J Surg Oncol 2013 Sep 4.
41. Palumbo BT, Henerson ER, Groundland JS, Cheong D, Pala E, Letson GD., Ruggieri P. Advances in segmental endoprosthetic reconstruction for extremity tumors: a review of contemporary design and techniques. Cancer Control 2011 Jul; 18(3): 160-70.
42. Flint MN, Griffin AM, Bell RS, et al. Aseptic loosening is uncommon with uncemented proximal tibia tumor prostheses. Clin Orthop Relat Res 2006; 450: 52-59.
43. Lazarov M, De Bo T, Poffyn B, Sys G. Radiologic Evaluation of Compressive Osseointegration for the Fixation of Reconstruction Prostheses after Tumor Resection. Biomed Res Int 2015; 2015: 513939.
44. Healey JH, Morris CD, Athanasian EA, Boland PJ. Compress knee arthroplasty has 80% 10-year survivorship and novel forms of bone failure. Clinical Orthopaedics and Related Research 2013; 471(3): 774-83.
45. Kay RM, Kabo JM, Seeger LL, et al. Hydroxyapatite-coated distal femoral replacements: preliminary results. Clin Orthop Relat Res 1994; 302: 92-100.
46. Bini SA, Johnston JO, Martin DL. Compliant prestress fixation in tumor prostheses: interface retrieval data. Orthopedics 2000; 23(7): 707-711; discussion 711-2.
47. Unwin PS, Cobb JP, Walker PS. Distal femoral arthroplasty using custom-made prostheses. The first 218 cases. J Arthroplasty 1993; 8: 259-68.
48. Unwin PS, Walker PS. Extendible endoprostheses for the skeletally immature. Clin Orthop Relat Res 1996; 322: 179-93.
49. Heisel C, Kinkel S, Bernd L, Ewerbeck V Megaprostheses for the treatment of malignant bone tumours of the lower limbs. International Orthopaedics (SICOT) 2006; 30: 452-7.
50. Coathup MJ, Batta V, Pollock RC, Aston WJ, Cannon SR, Skinner JA, Briggs TW, Unwin PS, Blunn GW. Long-term survival of cemented distal femoral endoprostheses with a hydroxyapatite-coated collar: a histological study and a radiographic follow-up. J Bone Joint Surg Am 2013 Sep 4; 95(17): 1569-75.
51. Plötz W, Rechl H, Burgkart R, et al. Limb salvage with tumor endoprostheses for malignant tumors of the knee. Clin Orthop Relat Res 2002; 405: 207-15.
52. Unwin PS, Cannon SR, Grimer RJ, Kemp HB, Sneath RS, Walker PS. Aseptic loosening in cemented custom-made prosthetic replacements for bone tumours of the lower limb. J Bone Jt Surg Br 1996; 78: 5-13.
53. Blunn GW, Briggs TW, Cannon SR, et al. Cementless fixation for primary segmental bone tumor endoprostheses. Clin Orthop Relat Res 2000; 372: 223-30.
54. Bickels J, Wittig JC, Kollender Y, Henshaw RM, Kellar-Graney KL, Meller I, Malawer MM. Distal femur resection with endoprosthetic reconstruction: a long-term followup study. Clin Orthop Relat Res 2002; 400: 225-35.
55. Mavrogenis AF, Papagelopoulos PJ, Coll-Mesa L, Pala E, Guerra G, Ruggieri P. Infected tumor prostheses. Orthopaedics 2011 Dec 1; 34(12): 991-8.
56. Hardes J, Ahrens H, Gebert C, Streitbuerger A, et al. Lack of toxicological side-effects in silver-coated megaprostheses in humans. Biomaterials 2007; 28(18): 2869-75.
57. Hardes J1, von Eiff C, Streitbuerger A, Balke M, Budny T, Henrichs MP, Hauschild G, Ahrens H. Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. J Surg Oncol 2010 Apr 1; 101(5): 389-95.
58. Funovics PT, Hipfl C, Hofstaetter JG, Puchner S, Kotz RI, Dominkus M. Management of septic complications following modular endoprosthetic reconstruction of the proximal femur. Int Orthop 2011 Oct; 35(10): 1437-4.
59. Moran E, Byren I, Atkins BL. The diagnosis and manage-

ment of prosthetic joint infections. J Antimicrob Chemother 2010; 65 Suppl 3: iii45-iii54.
60. Marculescu C, Berbari E, Hanssen A, et al. Outcome of prosthetic joint infections treated with debridement and retention of components. Clin Infect Dis 2006; 42: 471-8.
61. Mavrogenis AF, Pala E, Angelini A, Calabrò T, Romagnoli C, Romantini M, Drago G, Ruggieri P. Infected tumor prostheses: Clinical Outcomes of 100 Patients. Surg Infect (Larchmt) 2015 Mar 26.
62. Gosheger G, Hardes J, Ahrens H et al. Silver-coated megaendoprostheses in a rabbitmodel - an analysis of the infection rate and toxicological side effects. Biomaterials 2004; 25(24): 5547-56.
63. Donati F, Di Giacomo G, D'Adamio S, Ziranu A, Careri S, Rosa M, Maccauro G. Silver-Coated Hip Megaprosthesis in Oncological Limb Savage Surgery. Biomed Res Int 2016; 2016: 9079041.
64. Schmolders J, Koob S, Schepers P, Pennekamp PH, Gravius S, Wirtz DC, Placzek R, Strauss AC. Lower limb reconstruction in tumor patients using modular silver-coated megaprostheses with regard to perimegaprosthetic joint infection: a case series, including 100 patients and review of the literature. Arch Orthop Trauma Surg 2017; 137: 149-53.
65. Mavrogenis AF, Angelini A, Pala E, Sakellariou VI, Ruggieri P, Papagelopoulos PJ. Reconstruction of the extensor mechanism after major knee resection. Orthopaedics 2012 may 1; 35(5): e672-80.
66. Mavrogenis AF, Pala E, Angelini A, Ferraro A, Ruggieri P. Proximal Tibial Resections and Reconstructions: Clinical Outcome of 225 Patients. Journal of Surgical Oncology 2013; 107: 335-42.
67. Bickels J, Wittig JC, Kollender Y, et al. Reconstruction of the extensor mechanism after proximal tibia endoprosthetic replacement. J Arthroplasty 2001; 16: 856-62.
68. Malawer MM, Mchale KA: Limb-sparing surgery for high-grade malignant tumors of the proximal tibia: Surgical technique and a method of extensor mechanism reconstruction. Clin Orthop Relat Res 1989; 239: 231-48.
69. Abboud JA, Patel RV, Donthineni-Rao R, et al. Proximal tibial segmental prosthetic replacement without the use of muscle flaps. Clin Orthop Relat Res 2003; 414: 189-96.
70. Horowitz SM, Lane JM, Otis JC, et al. Prosthetic arthroplasty of the knee after resection of a sarcoma in the proximal end of the tibia. J Bone Joint Surg Am 1991; 73A: 286-93.
71. Eckardt JJ, Matthews JG, Eilber FR. Endoprosthetic reconstruction after bone tumor resections of the proximal tibia. Orthop Clin North Am 1991; 22: 149-60.
72. Yoshida Y, Osaka S, Ryu J. Reconstruction of the knee extensor mechanism in patients with a malignant bone tumor of the proximal tibia. Surg Today 2010; 40: 646-9.
73. Oddy MJ, Pendegrass CJ, Goodship AE, et al. Extensor mechanism reconstruction after proximal tibial replacement. J Bone Joint Surg Br 2005; 87: 873-78.
74. Gosheger G, Hillmann A, Lindner N, et al. Soft tissue reconstruction of megaprostheses using a trevira tube. Clin Orthop Relat Res 2001; 393: 264-71.
75. Bunchner M, Zeifang F, Bernd L. Medial gastrocnemius muscle flap in limb-sparing surgery of malignant bone tumors of the proximal tibia: Mid-term results in 25 patients. Ann Plastic Surg 2003; 51: 266-72.
76. Grimer RJ, Belthur M, Carter SR, et al. Extendible replacements of the proximal tibia for bone tumours. J Bone Joint Surg Br 2000; 82: 255-60.
77. Nystrom LM, Morcuende JA. Expanding endoprosthesis for pediatric musculoskeletal malignancy: current concepts and results. Iowa Orthop J 2010; 30: 141-9.
78. Dominkus M, Krepler P, Schwameis E, et al. Growth prediction in extendable tumor prostheses in children. Clin Orthop Relat Res 2001; 390: 212-20.
79. Lewis MM, Bloom N, Esquieres EM, et al. The expandable prosthesis. An alternative to amputation for children with malignant bone tumors. AORN J 1987;46: 457-70.
80. Eckardt JJ, Safran MR, Eilber FR, et al. Expandable endoprosthetic reconstruction of the skeletally immature after malignant bone tumor resection. Clin Orthop Relat Res 1993; 297: 188-202.
81. Neel MD, Wilkins RM, Rao BN, et al. Early multicenter experience with a noninvasive expandable prosthesis. Clin Orthop Relat Res 2003; 415: 72-81.
82. Schindler OS, Cannon SR, Briggs TW, et al. Stanmore custom-made extendible distal femoral replacements. Clinical experience in children with primary malignant bone tumours. J Bone Joint Surg Br 1997; 79: 927-37.
83. Wilkins RM, Soubeiran A. The Phenix expandable prosthesis: early American experience. Clin Orthop Relat Res 2001; 382: 51-8.
84. Letson GD, D'Amato G, Windham CT, et al. Extendable prostheses for the treatment of malignant bone tumors in growing children. Curr Opin Orthop 2003; 14: 413-8.

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