Outcomes and Options for Prosthetic Reconstruction After Tumour Resection About the Knee

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Abstract Endoprosthetic reconstruction after resection of a primary bone malignancy has become an established surgical modality that preserves the limb without compromising oncologic survival. Tumours arising from the proximal tibia and distal femur pose a unique set of challenges in the management of soft tissues and the restoration of limb length and joint kinetics. These issues are especially complex in the skeletally immature patient. The focus of this article is to review recent innovations in modern endoprosthetic design, with a focus on outcomes and treatment of surgical complications such as infection, aseptic loosening and extensor mechanism failure. We also review functional outcomes across various types of endoprosthetic designs.

Keywords Endoprosthetic reconstruction · Sarcoma · Growing prosthesis · Knee · Surgical outcomes · Complications

Introduction

Limb-sparing surgery (LSS) has become a conventional means of surgical management for patients with a primary bone malignancy as a result of advances in imaging technology, chemotherapy regimens and modern endoprosthetic implant design. Whereas in the past ablative surgery was considered the standard of care, indications for LSS have expanded over time and 90–95 % of these tumours are now salvageable with a variety of reconstructive options without oncologic compromise [1–5]. Overall survival in bone sarcoma patients as a result of these advances ranges from 61 to 92 % [2, 3, 6–9] and rates of local recurrence are reported as ranging from 0 to 16 % [3, 5, 8, 9]. Optimising function and preventing long-term complications after the appropriate oncologic treatment remains a challenge.

The knee is one of the most common locations for bone sarcoma [4, 10, 11]. Tumours arising from the proximal tibia and distal femur pose a unique set of challenges in the management of soft tissues and the restoration of limb length and joint kinetics. These issues become especially complex in the skeletally immature patient where predicting growth and leg length discrepancy can be imprecise, fraught with complications and accompanied by unrealistic patient and family expectations [4, 12••].

Over the years, innovation in implant design has moved from fixed to rotating hinge endoprosthetic replacements (EPR), custom to modular designs that may be cemented, press-fit or compressed, and a spectrum of invasive to non-invasive growing mechanisms. The goal of this review is to highlight the evolution of these implants, as well as the limitations, complications and functional outcomes that can be expected from this reconstructive option.

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Why Choose Endoprosthetic Replacement?

There is a gamut of viable surgical options for extremity bone sarcoma, including amputation, rotationplasty, irradiation/reimplantation, allograft/allograft-prosthetic composites and EPR. Less than 10 % of patients require amputation in modern patient series, and endoprostheses have become the most conventional form of reconstruction [1–3, 9]. Oncologic outcome, quality of life, function and cost each play a role in selecting the best reconstructive option, as does surgeon and patient preference.

When amputation has been compared with LSS in observational studies, a significant number report better function, lower lifetime cost and similar oncologic outcomes in patients treated with LSS [1–5, 12•, 13–16]. However, these functional outcome findings are mitigated by relatively small patient cohorts, a heterogeneous group of limb-salvage procedures and frequent selection bias as those undergoing amputation often have more extensive disease and potentially more biologically aggressive tumours. Additionally, very few studies directly compare amputation to EPR.

In a large, multicentre review of 227 cases of distal femoral osteosarcoma, Rougraff et al. [5] reported superior functional outcomes (MSTS, Knee Society score) in LSS patients as compared to amputation, despite a 41 % reoperation rate in the LSS group. Thirty-four of the 73 LSS patients were treated with an EPR. The Scandinavian Sarcoma Group reported on 118 patients with extremity bone sarcoma treated with LSS compared with amputation with a mean follow-up of 13 years. Ninety-four of these patients had tumours located in the femur or tibia and 57 % were managed with LSS. TESS scores, rates of employment and physical activity level were found to be equivalent in both groups, whereas quality of life, as measured by the SF-36, was found to be significantly in favour of LSS patients in the domains of physical function and bodily pain although the overall SF-36 was not significantly different between the two groups. Nearly all patients with very poor function (MSTS <50 %) were amputee patients [1]. The most recent comparison of amputation and EPR in bone sarcoma about the knee was a study by Malek et al. [17•], who demonstrated better reintegration to normal living index and Physiological Cost Index (PCI) scores (a validated measure of the oxygen cost of walking) amongst EPR patients at a median 56-month follow-up. They were, however, unable to detect a difference in perceived quality of life, TESS or SF-36 scores. Although a small study with retrospective design, this is one of the few comparison studies evaluating EPR alone as the limb-salvage procedure in the distal femoral and proximal tibial sarcoma with a number of functional outcome measures.

In cost-effectiveness studies, evidence points to amputation and rotationplasty being more expensive over a

patient's lifetime as a result of external prosthetic devices, despite the increased number of surgical interventions in patients managed with an implant [18•, 19]. Grimer et al. [19] derived a formula to calculate the total cost of amputation compared to non-extendible EPRs, taking into account index procedure cost, years of follow-up and outpatient expenditures, as well as the risk and cost of “servicing” and revision procedures. Nearly eightfold in savings were projected with the use of an EPR over 20 years. Gait analysis studies have also documented improved gait patterns and reduced oxygen consumption in patients treated with an EPR [17•, 20–22]. One multi-centre, cross-sectional study of bone sarcoma located around the knee demonstrated better TUDS (time walking up and down stairs) and VMA walking tests in LSS patients under the age of 25 years, but no difference in TESS score, PCI or Baecke indices for sport, leisure and work function [23•].

Endoprosthetic reconstruction has been associated with a significant rate of complications requiring revision over time, although these figures have diminished since the introduction of modern implants [4, 5, 10, 11]. Some evidence points to rotationplasty being a more durable reconstruction, but this is also mitigated by complications such as fracture, vascular compromise, malrotation as well as issues around cosmesis and body image [24–26].

Controversies and Advances in Implant Design

In early prosthetic designs, implants around the knee used a fixed hinge, fully constrained prosthesis. In our centre, the implant (based on a Stanmore knee replacement) was fitted with a central axis and small articulated tibial pin (Stanmore Implants, Elstree, UK), the latter of which was prone to wear [9]. Over time, this was replaced with a rotating hinge mechanism in order to decrease the rotational stress on the implant and polyethylene bushings [9, 27, 28]. The original implants were made of titanium alloy, but in the tibia in particular, this led to significant metallosis in the soft tissues. The implants were subsequently coated with a titanium nitride so as to increase resistance to wear and corrosion, which successfully reduced this occurrence. A hydroxyapatite collar was added at the junction of the prosthesis with the stem to promote bone ingrowth [9, 29•]. Myers et al. reported a series of 194 patients with a proximal tibial sarcoma that demonstrated a reduction in rates of aseptic loosening from 46 to 3 % at 10 years with the adoption of a modern rotating hinge design [11]. There was also a risk reduction of over 50 % in reoperation for any reason at 15 years follow-up. Similarly, in distal femoral EPRs, our centre reported our 30-year experience across 335 patients and found a risk reduction of 52 % with

Fig. 1 Major innovations in implant design since the inception of endoprosthetic replacement (EPR)

the use of a rotating hinge implant with a hydroxyapatite (HA) collar [10]. Causes of failure in the rotating hinge implant were infection and stem fracture, whereas aseptic loosening was most commonly associated with failure and revision in the fixed hinge prosthesis. The major advances in endoprosthetic design over the past few decades are detailed in Fig. 1.

Cement, Press-Fit or Compress?

Good to excellent results have been obtained in both cemented and uncemented implant designs; however, the rate of surgical complications and revisions remains high in both. A third generation cementing technique is typically employed, and reaming allows for a 1–2-mm cement mantle. The rotational forces on the prosthesis are mitigated by the use of the rotating hinge, an anti-rotation lug and an HA-coated collar. Our centre has reported implant survival of cemented stems in distal femoral prostheses of 83, 67 and 42 % at 5, 10 and 20 years, respectively, and in the proximal tibia, 88, 75 and 70 % at 5, 10 and 15 years, respectively [10, 11]. These figures are similar in other series [30, 31•, 32•, 33].

The use of HA collars has been developed for both cemented and uncemented stems (Fig. 2), and has been shown to promote bony ingrowth and decrease the rates of aseptic loosening by stabilising the stem and cement mantle and preventing the tracking of osteolytic wear debris down the canal [29•, 34, 35•, 36, 37]. Chao et al. [34] reported the long-term results of 59 patients treated at

Fig. 2 Proximal tibial endoprosthetic replacement with hydroxyapatite collar

the Mayo Clinic with extra-cortical bone bridging and ingrowth fixation of a porous coated stem. Porous coating of titanium fiber metal or cobalt-chromium beads at the implant shoulder was combined with allo- or autografting at the bone-implant interface at the time of implantation.

The majority of stems were cemented, with the exception of seven. Overall, there was no difference in bony ingrowth radiographically between cemented and uncemented stems as measured in four zones ($87 \% \pm 26$ vs. $67 \% \pm 32$, $p = 0.29$), and stem loosening occurred in only two stems in one arthrodesis patient. Finite element analyses support increased stem and cement mantle stability secondary to this technique [37]; however, retrieval studies were not originally able to correlate radiographic bone ingrowth with osseous integration histologically [38]. In 2013, Coathup et al. [29•] presented the long-term survival of cemented Stanmore distal femoral EPRs with an HA collar. The authors found evidence of mature lamellar bone within the HA-collar grooves on light microscopy as compared to fibrous tissue in a small comparative group of EPRs retrieved with no collar. Seventy per cent of stems were ingrown radiographically; however, there was no significant difference in the overall survival in collars showing ingrowth versus those that did not, and as such, the clinical significance is still unknown.

Uncemented stems were developed in the hopes of promoting biologic ingrowth, and increased stability and longevity of EPRs. A fully porous coated anchorage stem and splines are present in some designs to neutralise the rotational forces at the bone-implant interface, and under-reaming by 0.5 mm helps to create a press-fit of the implant into cortical bone [39]. The Kotz Modular Femur and Tibia Resection System (KMFTR; Howmedica, Stryker, Osteonics, Rutherford, NJ) is a fixed-hinge implant, which initially had holes and a side plate for cross-fit screws; however, this was abandoned secondary to increased rates of stress shielding [40]. Similar to cemented prostheses, aseptic loosening, implant breakage and infection are common modes of long-term failure [39]. However, some series have reported decreased rates of aseptic loosening [28, 39–41]. Flint et al. [40] reported no cases of aseptic loosening in 44 consecutive patients treated with an uncemented proximal tibial EPR at a mean of 60 months (range 9–162). The functional scores analysed showed a mean TESS score of 75 and a mean MSTs of 25. A specific concern of uncemented stems revolves around the period of postoperative chemotherapy where little bony ingrowth occurs. Weight-bearing protocols vary between centres, and some elect to protect weight-bearing for 12 weeks during this period of adjuvant treatment, which may be disadvantageous for patients [40]. No consensus, however, exists regarding postoperative weight-bearing status, and a significant amount of variability between centres' postoperative protocols was observed.

Concern over the high rates of complications in both cemented and uncemented endoprostheses led to the development of an alternative biologically fixed implant, the Compress® Compliant Pre-Stress Implant (Biomet,

Warsaw, IN), which attempts to achieve stem fixation by compressing stored energy through a short traction bow secured with transverse pins [43•]. Theoretically, this design promotes osseous integration by inducing bone hypertrophy, prevents stress shielding and blocks the migration of wear debris into the canal [43•]. Medium-term results have been promising, and these implants may be especially useful in resections that leave a short segment for stem fixation. A matched case-control study of 52 cemented distal femoral EPR patients from our centre and the University of California San Francisco showed similar rates of device-related failure (1 of 26 in each cohort) in early follow-up. The rate of revision for all causes in each group was 7.7 % at 2 years [44]. Reasons for failure included fracture of the tibial stem in the cemented EPR group and failure of the compression mechanism in the Compress group. A follow-up study of the same patient cohort found evidence of aseptic loosening in two additional patients in the cemented EPR group, but no difference in 5-year implant survival [Compress®, 95.7 % (95 % CI, 0.73–0.99); Stanmore, 91.3 % (95 % CI, 0.69–0.98)] [43•]. Farfalli et al. [42] have also compared the Compress® with press-fit EPRs in a retrospective series of 91 patients. They reported no difference in 5-year prosthetic survival (85 vs. 88 %, $p = 0.9$) or the number of failures. Uncemented prostheses failed primarily because of aseptic loosening, as well as a stem fracture in one patient; the Compress® failed as a result of femoral fracture and distal bone resorption at the compression site. Stem diameter less than 13.5 mm was associated with decreased implant survival in the press-fit group. While short- and medium-term outcomes are encouraging, longer-term follow-up with larger patient cohorts are needed to assess the durability of this implant.

Modular Versus Custom EPR

Custom-designed implants are available for both distal femur and proximal tibial endoprostheses, and their use varies by institution. In our centre, the majority of patients with a primary bone tumour will receive a custom EPR. Radiographic protocol films are taken prior to commencing neoadjuvant treatment. The level of resection is determined based on the initial staging studies, and an implant is ordered. Repeat staging prior to surgery is required to ensure that there has been no change in tumour extent. It is most unusual for there to be a significant change in the extent of tumour within the bone, but nonetheless, care must be taken to carry out the appropriate level of resection in these scenarios.

Modular designs are also available and used in many centres for both metastatic disease and primary bony sarcoma. In 2010, Schwartz et al. [32•] reported a trend

toward improved implant survival in 29 modular implants compared to 23 custom-designed proximal tibial prostheses. However, the custom implants dated from 1985 to 1989, while modular components were more modern designs. Similar findings were reported in their series of 186 distal femoral EPRs; however, the custom-made, one-piece casted implants also dated back before the 1990s [31•]. Other centres using both modular and custom systems have reported similar implant-related survival [45–49], although to our knowledge no direct comparisons of modern implants have been carried out.

Growing Implants

Scales and Sneath [50] were the first to describe expandable prostheses in the skeletally immature patient with bone sarcoma. This population is difficult to treat secondary to the imprecision of predicting limb length and the longevity required of these implants [51•, 52–54]. There have been tremendous changes in the design of these constructs since their inception (Fig. 3), predominantly as a result of the considerable complication rates. Open lengthening procedures were the standard in early designs, but we have progressively moved toward minimally invasive techniques so as to prevent major soft tissue dissection and infection as a result of multiple procedures. Non-invasive expandable implants are a novel means of eliminating surgical intervention to achieve limb length [55]; electromagnetic induction can be used in an outpatient setting for EPR lengthening.

Fig. 3 Expandable total femoral replacement. This picture shows a minimally invasive growing implant, now fully expanded and explanted as patient required conversion to an adult prosthesis

Mixed results have been reported. Ruggieri et al. [56•] compared the minimally invasive Kotz Growing prosthesis (Howmedica Modular Reconstruction System, Stryker, UK) with two non-invasive designs, the Stanmore noninvasive expandable prosthesis (Extendable Mark V, Stanmore Implants Worldwide, Stanmore, Middlesex, England, UK) and the Repiphysis (Wright Medical Technologies, Arlington, TN) in 32 children and found that the Repiphysis was associated with a higher rate of complications and shorter survival when compared to the Kotz prosthesis. Overall, one-third of patients who achieved skeletal maturity had equivalent limb length, while two-thirds had a discrepancy between 15 and 30 mm. Despite a complication rate of 50 % overall, patients reported good function, and MSTs scores were not significantly different across the implant groups. Multiple series have now shown high rates of complications with the Repiphysis, specifically with implant breakage [57•, 58•, 59, 60]. Picardo et al. [61•] reviewed 55 children who underwent reconstruction with a non-invasive Stanmore expandable endoprosthesis; the mean lengthening achieved was 38.6 mm (range 3.5–161.5) after a mean of 11 procedures per patient. Complications occurred in 29 % of patients, and 18 % required a revision. A high rate of infection (18 %) was documented in one series of 34 children treated with a non-invasive growing implant at medium-term follow-up [62•]. Device-related complications were identified as failure of the growing mechanism and scar tissue formation.

Henderson et al. [12•] point out that by excluding expected revision for lengthening purposes, the rate of failures is similar between adult implants and extendable implants. Henderson also found a nearly 40-fold lifetime increase in private insurance reimbursement for surgical versus non-surgical lengthening procedures [18•]. Mean cost of reimbursement for a single surgical lengthening procedure was \$9,950 (range, \$4,897.29 USD to \$12,166.39 USD) versus \$272 for an outpatient lengthening. Increased cost was associated with males, who reach skeletal maturity later in adolescence, as well as distal femoral location, which has the greatest potential for growth consequently requiring additional lengthening procedures [18•]. While based solely on US cost estimates, these results are compelling. Further research into the total costs, rehabilitation and follow-up, as well as cost of maintenance procedures and revision surgery for complications, should be the focus of future research in this patient subgroup.

Surgical Complications: What to Expect

While endoprosthetic replacement has become an established method of limb salvage and innovation in

biomedical engineering has significantly improved upon patient outcomes, a significant number of surgical complications can be expected. In particular, mid- and long-term complications such as infection, aseptic loosening, mechanical failure and secondary amputation significantly limit the success of EPR reconstruction about the knee [44] (Table 1). Lymphedema, extensor mechanism failure and chronic pain also contribute to poor outcomes in this patient population. Henderson and colleagues have classified segmental endoprosthetic failure using a multi-institutional review of five centres' outcomes following EPRs. They observed 534 failures in 2,174 (24.6 %) patients over 34 years. Forty-four per cent involved the distal femur, 14 % the proximal tibia and 2 % both. Types of failure were classified as mechanical (49 %) and non-mechanical causes. Modes of mechanical failure were labelled as type 1, soft tissue failures such as instability, tendon rupture and wound dehiscence; type 2, aseptic loosening; and type 3, structural failure such as implant or periprosthetic fracture. Non-mechanical modes of failure were characterised as type 4, infection requiring explantation, and type 5, tumor recurrence or progression with implant contamination [63•]. These complications can be severe, some requiring secondary amputation [9–11, 30, 31•, 32•, 33].

Infection

Infection around any orthopaedic implant can be problematic, but particularly so in patients undergoing LSS with a massive endoprosthesis. Significant host and treatment factors place the patient at elevated risk; immunocompromise in those on chemotherapeutic regimens, extensive soft tissue resection requiring muscle flap reconstruction, lengthy surgical times and radiotherapy in select patients can have disastrous consequences for the limb. Deep infection has ranged from 5 to 34 % in multiple patient series, with secondary amputation in up to 26 % [5, 9, 11, 15, 31•, 32•, 63•, 64, 65•, 66•, 67•, 68•, 69, 70]. Antibiotic prophylaxis, laminar flow operating rooms, antibiotic-impregnated cement and screening for resistant bacterial organisms have not significantly mitigated this risk [71•]. The Japanese Musculoskeletal Oncology group recently reported an infection rate of 14.6 % in 388 EPRs for tumours about the knee [67•]. Cultured organisms were most commonly *Staphylococcus aureus*, MRSA and *Staphylococcus epidermidis*. Risk factors for infection were poor soft tissue coverage, extra-articular resection and cases presenting with drainage or frank pus. Cho and colleagues assessed causes of infection in the proximal tibia and found that resection of greater than 37 % or 12.5 cm of the overall tibial length significantly increased the risk of deep infection [65•]. Multiple studies have found that infection risk is significantly decreased with the routine use

of a gastrocnemius flap when reconstructing the extensor mechanism [9, 72, 73•, 74•]. Options for larger soft tissue defects or aseptic wound complications such as dehiscence or delayed healing that cannot be managed with primary skin closure, rotational flaps or skin grafting include free muscle flaps.

Antibiotic Prophylaxis

International consensus on the type and duration of the prophylactic antibiotic regimen in this patient population is currently lacking and is the focus of a multicentre randomised trial (PARITY) [75•]. In routine arthroplasty, one dose preoperatively followed by 24 hours of gram-positive coverage with a cephalosporin is standard. However, a recent survey of members of the Musculoskeletal Tumor Society and the Canadian Orthopaedic Oncology Society suggests that there is wide variability in prescribing practices: 73 % prescribe a first generation cephalosporin, while 25 % use an additional aminoglycoside or Vancomycin, with variability in duration and dosing [75•]. Others have recommended maintaining antibiotic coverage until the drains are removed, which can be up to 6 or 8 days [32•]. Surgical site infections have consistently posed a significant threat to implant and limb survival, and the development of antibiotic-resistant strains makes this matter all the more pressing.

Implant Coating: Silver or Iodine?

A variety of implant-related solutions have been proposed to decrease infection rates in EPRs. Silver-coated prostheses have shown excellent promise and are now used in nearly all revision EPRs for sarcoma and revision arthroplasty patients in our centre. Silver is bactericidal against a range of bacteria. In vitro and animal studies have shown it to be efficacious against *Staphylococcus epidermidis* species and to reduce the risk of infection in silver-coated EPRs in a rabbit model [76•, 77•, 78]. A prospective cohort study of 125 sarcoma patients treated with an EPR showed a reduction in the incidence of deep infection in silver-coated prostheses as compared to uncoated titanium EPRs (17.6 vs. 5.9 %, $p = 0.062$). Five of 16 patients (38.5 %) with deep infection in the uncoated titanium group required an amputation versus none in the silver-coated group at medium-term follow-up [71•]. Findings in our centre are similar; we have recently presented our data on silver-coated EPRs at the International Society of Limb Salvage and found over 77 % risk reduction in positive cultures at second stage revision in a matched case-control study of 84 patients with a silver-coated versus non-coated titanium EPR (ISOLS, Bologna, Italy, 2013). Hussman et al. [76•] investigated the silver ion concentration in serum and in

Table 1 Outcomes, complications and survival in major distal femoral and proximal tibial endoprosthetic reconstruction series

Study	Site	Population	Mean follow-up (y)	Overall survival	Implant survival	Aseptic loosening	Infection	Secondary amputation	Any cause revision	Functional outcome	Type of study
Myers et al. [10]	PT	n = 194 FH: 95 RH: 99	14.7	59 %	68, 39, 25 % (5, 10, 20 y)	FH: 46 % (10 y) RH: 3 % (10 y) (p < 0.0001)	19.5 % No gastroc flap: 31 % Gastroc flap: 14 % (p = 0.0136)	17.5 %	FH: 32, 61, 75 % (5, 10, 20 y) RH: 12, 25, 30 % (5, 10, 15 y)	NR	Retrospective review of prospectively collected data
Myers et al. [11]	DF	n = 335 FH: 162 RH: 173	12	57.3 %	83, 67, 42 % (5, 10, 20 y)	FH: 35 % RH: 24 % (10 y)	9.6 %	10.7 %	24 %	NR	Retrospective review of prospectively collected data
Pedtke et al. [43••]	DF	n = 52 CPS: 26 CM: 26	6.2	82.7 %	CPS: 83.5 % CM: 66.6 % (5 y) (p < 0.0001)	CPS: 3.8 % CM: 11.5 % (p = 1.00)	CPS = 0 % CM: 7.7 % (p = 0.49)	CPS: 11.5 % (infection) CM: 11.5 % (3.8 % infection; 7.7 % LR)	CPS: 7.7 % CM: 15.3 % (p = 0.67)	NR	Matched case-control
Cho et al. [65•]	PT	n = 62 FH: 18 RH: 44 CM: 12 UCM: 50	8.2	NR	76.7 % (5 y) 73.9 % (10 y)	NR	25.8 % Associated with >37 % or 12.5 cm tibial resection	3/62 (4.8 %)	NR	MSTS 24.2 FH: 24.6 RH: 25.8	Retrospective
Jentzsch et al. [86•]	PT	n = 16	5	87.5 %	NR	1/16 (6.25 %)	1/16 (6.25 %)	NR	NR	NR	Retrospective
Mori et al. [67••]	Infected DF/PT	n = 57	5.5	NR	76.9 % (5, 10 y)	NR	14.6 %	11/57 (19 %)	NR	NR	Retrospective
Mavrogenis et al. [68••]	PT	n = 225 FH: 165 RH: 60 CM: 16 UCM: 209	7.5	62 % (10 y)	FH: 82, 78 % (5, 10 y) RH: 78 % (5 y) (p = 0.806)	FH: 6 % RH: 5 %	12 %	7 %	NR	MSTS 76 % Better in RH (p = 0.042)	Retrospective review of prospectively collected data
Pala et al. [82••]	Lower limb DF: 199 PT: 60	n = 281	4.2	88 %	DF: 66, 58 % (5, 8 y) PT Primary: 49, 36 % (5, 8 y) Revision: 90, 90 % (5, 8 y) (p = 0.0410)	DF: 5.5 % PT: 6.7 % Primary: 4.6 % Revision: 6.1 %	10 %	0.4 %	DF Primary: 29.3 % Revision: 21.9 % PT Primary: 42.8 % Revision: 9.1 %	MSTS: 24.5 Primary: 25 Revision: 23.9	Retrospective review of prospectively collected data

Table 1 continued

Study	Site	Population	Mean follow-up (y)	Overall survival	Implant survival	Aseptic loosening	Infection	Secondary amputation	Any cause revision	Functional outcome	Type of study
Henderson et al. [63••]	All sites, multicentre DF: 951 Combined DF/PT: 44 PT: 298	n = 2174	NR	NR	DF: 73 % Combined DF/PT: 57 % PT: 66 %	DF: 6.8 % Combined DF/PT: 2.3 % PT: 4.7 %	DF: 8.3 % Combined DF/PT: 22.7 % PT: 15.1 %	NR	DF: 27 % Combined DF/PT: 43 % PT: 34 %	NR	Retrospective review of prospectively collected data
Jeys et al. [30]	All sites	n = 661 DF: 228 PT: 136	9	52.7, 45.7 % (10, 20 y)	DF: 52.7, 30.5 % (10, 20 y) PT: 39.9, 20.7 % (10, 20 y)	DF: 13.6 % PT: 12 % (p = 0.04)	DF: 12.7 % PT: 21 %	DF: 9.2 % PT: 18.4 %	DF: 47.3 % (10 y) PT: 60.1 % (10 y)	NR	Retrospective review of prospectively collected data
Kawai et al. [28]	DF/PT	n = 32 DF: 25 PT: 7	NR	NR	DF: 88 % PT: 58 % (5 y)	3.1 %	6.25 %	3.1 %	21.9 %	ISOLS: 27 HSSKS: 80	Retrospective review of prospectively collected data
Coathup et al. [29••]	DF	n = 61 CM with HA collar	8.5	83.6 %	75, 84.4, 88.5 % (5, 10, >10 y)	8 % (18 y)	3 % (18 y)	10 % (LR)	15 %	NR	Retrospective review of prospectively collected data
Schwartz et al. [31•]	DF	n = 186 CM modern modular: 85 CM older custom: 101	8	65 %	Overall: 77.2, 57.9, 50.2 % (10, 20, 25 y) Custom: 51.7 % Modular: 93.7 % (15 y) (p = 0.0011)	10.2 %	3.2 %	9.7 %	18.8 %	MSTS: 26 (86.7 %)	Retrospective
Schwartz et al. [32•]	PT	n = 52 CM modern modular: 29 CM older custom: 23	8	75 %	94, 86, 66, 37 % (5, 10, 15, 20 y) Custom: 63 % Modular: 88 % (15 y) (p = 0.13)	11.5 %	5.8 %	9.6 %	19.2 %	MSTS: 24.6 (82 %)	Retrospective
Flint et al. [40]	PT	n = 44 UCM	5	NR	NR	0 %	16 %	NR	27 %	TESS: 77 MSTS: 25 (75 %)	Retrospective

Table 1 continued

Study	Site	Population	Mean follow-up (y)	Overall survival	Implant survival	Aseptic loosening	Infection	Secondary amputation	Any cause revision	Functional outcome	Type of study
Griffin et al. [41]	DF/PT UCM	n = 99 DF: 74 PT: 25	NR	NR	NR	7 %	10 %	NR	25 %	NR	Retrospective
Farfalli et al. [42]	DF	n = 91 UCM: 50 CPS: 41	UCM: 7.3 CPS 3.75	NR	UCM: 85, 71 % (5, 10 y) CPS: 88 % (5 y) (p = 0.9)	12.1 %	NR	NR	UCM: 26 % CPS: 12.1 % (p = 0.1) Stem diameter <13.5 associated with lower implant survival (p = 0.037)	MSTS: 25.7 UCM: 25.7 CPS: 26.8	Retrospective
Jeys et al. [40]	All sites	n = 1261 DF: 492 Tibia: 245	6,507 patient-y	60, 54, 40 % (5, 10, 20 y)	NR	NR	NR	Overall: 8.9 % DF: 8.5 % Tibia: 15.5 % Higher in tibia than other sites (p = 0.001)	NR	NR	Retrospective review of prospectively collected data
Hardes et al. [71••]	PF/PT	n = 125 Ag = 51 (PT: 29) Ti = 74 (PT: 41)	Ag: 19 mo Ti: 4.5	9.8 %	NR	NR	Ag: 6.9 % Ti: 17.1 % (p = 0.289)	Ag: 0 % Ti: 57 %	Ag: 3 % Ti: 32 % (p = 0.015)	NR	Retrospective

PT Proximal tibia, DF distal femur, FH fixed hinge, RH rotating hinge, HA hydroxyapatite collar, NR not reported, CPS Compress[®], CM cemented, UCM uncemented, LR local recurrence, MSTS Musculoskeletal Tumour Society score, ISOLS International Society of Limb Salvage, HSSKS Hospital for Special Surgery Knee Scoring System, TESS Toronto Extremity Salvage Score, Ag silver-coated EPR, Ti uncoated titanium EPR, y years, mo months

periprosthetic fluid from wound drains in 16 patients following implantation of a silver-coated EPR. Their findings also supported decreased incidence of infection in silver-coated implants, although drain fluid and serum values were not correlated with reinfection rates. No toxic effects of silver have yet been described at the levels seen in EPRs, although 23 % of patients were found to have local argyria in one study after implantation of a silver-coated EPR (Implantcast, Buxtehude, Germany) [79••]. The added cost of silver coating in our centre is 530£ (\$852 USD) per standard principal EPR shaft (Stanmore Implants, Elstree, UK).

Tsuchiya et al. [80•, 81••] have proposed iodine surface coating as a means of diminishing infection risk, whereby anodization of the implant creates an adhesive bactericidal oxide film of 5–10- μ m. Iodine-coated titanium demonstrates good biocompatibility and superior antibacterial properties compared with titanium and stainless steel in a rabbit model when exposed to *Staphylococcus aureus* and *Escherichia coli* [80•]. A heterogeneous series of 222 patients were treated with an iodine-coated implant and followed for a mean of 18.4 months (range 3–44); 32 patients had a megaprosthesis for tumour [81••]. Two per cent developed an infection in those treated prophylactically with an iodine-coated implant; no implant removal was required. No adverse thyroid function was observed for the study duration. Long-term follow-up of these metallic-coated prostheses is clearly needed as well as careful documentation of adverse systemic events; however, they show early promise in modifying infection risk.

Aseptic Loosening

Aseptic loosening is one of the most common causes of late implant failure, along with infection, and has been the subject of much scrutiny and research (Fig. 4). In a large series of 295 patients, a type 2 failure occurred in 4.5 % of primary EPRs and 6.1 % in revision cases; mean time to failure was 2.6 and 3.1 years, respectively [82••]. The distal femur showed the highest rate of type 2 failures. Henderson et al. found aseptic loosening to be the second most common mode of failure across EPRs in both the upper and lower extremities in a large multicentre series of 2,174 patients. Fixed hinge prostheses showed an increased incidence of aseptic loosening compared to rotating hinge mechanisms ($p = 0.0004$) [63••], which is consistent with the results of other major series in the literature. As previously discussed, much innovation has occurred at the level of implant design so as to minimise this complication. In a retrospective series of proximal tibial EPRs, Schwartz et al. [32•] reported a 19 % revision rate, 60 % of which were secondary to aseptic loosening at a mean of 11.8 years. They also reported high rates of failure after

converting a porous-coated ingrowth surface on the tibia to a smooth design, and this was quickly abandoned. Other innovations have included the addition of an HA collar to achieve biological fixation in both cemented and uncemented implants.

Extensor Mechanism Failure

Failure of the extensor mechanism can have a significant impact on patient function. In proximal tibial resections, the patellar tendon is sectioned 1–2 cm from its insertion on the tibial tubercle for oncologic margins [68••]. Achieving the appropriate patellar height, tendon fixation and healing to the implant can be problematic. Synthetic materials, such as the Trevira tube (Implantcast, Germany) and artificial ligaments, were used independently in previous series; however, high rates of infection led to routine rotational gastrocnemius flaps for implant coverage [9, 51••, 72, 83, 84•]. This was first described by Dubousset et al. [72] and involves detaching and transposing the medial head of the gastrocnemius muscle (plus or minus the hemi-soleus) to cover the implant. The patellar tendon and joint capsule are then repaired to the leading edge of the muscle with non-absorbable sutures followed by skin grafting if necessary. The patients' flexion is limited in the initial postoperative period so as to optimise healing and

Fig. 4 Aseptic loosening in a rotating hinge prosthesis; (a) aseptic loosening seen on a long leg radiograph of a distal femoral endoprosthesis; (b) significant osteolysis around the distal femoral stem

prevent an extensor lag; some have recommended splinting the knee in extension for 4 weeks; others recommend a short period of non-weight bearing [11, 51•, 85•, 86•]. Schwartz et al. [32•] reported a mean extensor lag of 17.9° in 52 patients with a proximal tibial EPR; however, passive ROM was full and the authors surmised that recurvatum was prevented by the extensor stop mechanism on the femoral side of the prosthesis. MSTS scores were 82 % despite the lack of extensor power. In our centre, patients are allowed to bear weight immediately postoperatively, but are limited to 60° of flexion for 6 weeks.

The Rizzoli Institute reported a 3 % incidence of extensor mechanism rupture in a large series of 225 patients. Mean extensor lag was 12°; however, the type of extensor mechanism repair, how it was attached to the implant and any augmentation were not found to be associated with MSTS score [68•]. Jentzsch et al. [86•] found that a significant number of patients developed patella alta within 2 years of index surgery in a small series of 14 patients; this was associated with extensor lag (mean, 17°) and reduced MSTS scores. Although more common in the proximal tibia, complications involving the extensor mechanism can equally affect patients with distal femoral sarcomas. Schwab et al. [87] found that 63 % of patients undergoing distal femoral reconstruction after sarcoma resection had patellar complications, ranging from impingement and patella baja to osteonecrosis and fracture. Impingement and patella baja were associated with worse ISOLS scores. One study reported an increase in isokinetic muscle strength compared to the contralateral limb in patients with a distal femoral resection with patellar resurfacing relative to those without [88]. However, overwhelming evidence for patellar resurfacing at index surgery is lacking and is not routinely performed in our institution.

Functional Outcomes in the Knee

Oncologic outcomes have proven to be similar in ablative and limb-salvage procedures, and as such, the focus of research has shifted to optimising patient function and quality of life. The young patient population treated for sarcoma is of particular interest as they are living longer, placing increased demands on their implants, and have higher expectations of their reconstructions. Gait analysis has gained in popularity, and in 2013, Okita et al. [89•] compared eight patients with endoprostheses about the knee with eight matched healthy subjects. They demonstrated increased negative joint forces and compensation in the ipsilateral ankle, contralateral knee and bilateral hips during gait analysis. Jentzsch et al. [86•] found that patella alta after proximal tibia resection, as measured by the

Blackburn-Peel Index, was associated with inferior functional outcome. Functional outcome scores have ranged from a mean MSTS of 61–90 % across a number of large series [9–11, 16, 30, 31•, 32•, 33, 64, 65•, 82•]. Recently, Pala et al. [82•] reported a difference in mean MSTS scores between primarily implanted and revision EPRs (25 vs. 23.5) across a series of 229 patients. Henderson et al. [12•] reported the functional outcomes of 27 patients with a growing prosthesis about the knee; emotional acceptance and paediatric outcomes data collection instrument (PODCI) happiness domains were high and were not significantly associated with complications. The physical function domains of the MSTS and PODCI were the lowest scores for any domain, but were not different across implant manufacturer or based on the tumour location. Quality of life indicators are under development, but early findings have not shown a significant difference amongst different endoprosthetic reconstruction techniques.

Conclusions

Endoprosthetic reconstruction after resection of distal femoral and proximal tibial primary bone malignancies is an oncologically safe method of preserving the limb and optimising patient function and quality of life. Innovation in implant design has led to a significant reduction in implant-related complications, and a variety of prosthetic options show similar results. However, implant revision rates remain high over long-term follow-up for a host of reasons. As such, anticipated outcomes and expectations of function and quality of life following tumour resection should be discussed in detail with patients and their families prior to embarking on any reconstructive surgery.

Compliance with Ethics Guidelines **Conflict of Interest** This work is supported in part by Cedars Cancer Institute and McGill University Health Centre. Krista A. Goulding, Czar Louie Gaston and Robert J. Grimer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as

- Of importance
- Of major importance

1. Aksnes LH, Bauer HC, Jebsen NL, Folleras G, Allert C, Haugen GS, et al. Limb-sparing surgery preserves more function than

- amputation: a Scandinavian sarcoma group study of 118 patients. *J Bone Joint Surg Br.* 2008;90(6):786–94.
2. Bacci G, Ferrari S, Bertoni F, Ruggieri P, Picci P, Longhi A, et al. Long-term 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(24):4016–27.
 3. Ferrari S, Smeland S, Mercuri M, Bertoni F, Longhi A, Ruggieri P, et al. Neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with localized osteosarcoma of the extremity: a joint study by the Italian and Scandinavian Sarcoma Groups. *J Clin Oncol.* 2005;23(34):8845–52.
 4. Grimer RJ. Surgical options for children with osteosarcoma. *Lancet Oncol.* 2005;6(2):85–92.
 5. 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(5):649–56.
 6. Elomaa I, Blomqvist CP, Saeter G, Akerman M, Stenwig E, Wiebe T, et al. Five-year results in Ewing's sarcoma. The Scandinavian Sarcoma Group experience with the SSG IX protocol. *Eur J Cancer.* 2000;36(7):875–80.
 7. Fuchs B, Valenzuela RG, Inwards C, Sim FH, Rock MG. Complications in long-term survivors of Ewing sarcoma. *Cancer.* 2003;98(12):2687–92.
 8. Wilkins RM, Cullen JW, Odom L, Jamroz BA, Cullen PM, Fink K, et al. Superior survival in treatment of primary nonmetastatic pediatric osteosarcoma of the extremity. *Ann Surg Oncol.* 2003;10(5):498–507.
 9. Grimer RJ, Carter SR, Tillman RM, Sneath RS, Walker PS, Unwin PS, et al. Endoprosthetic replacement of the proximal tibia. *J Bone Joint Surg Br.* 1999;81(3):488–94.
 10. Myers GJ, Abudu AT, Carter SR, Tillman RM, Grimer RJ. Endoprosthetic replacement of the distal femur for bone tumours: long-term results. *J Bone Joint Surg Br.* 2007;89(4):521–6.
 11. Myers GJ, Abudu AT, Carter SR, Tillman RM, Grimer RJ. The long-term results of endoprosthetic replacement of the proximal tibia for bone tumours. *J Bone Joint Surg Br.* 2007;89(12):1632–7.
 12. •• Henderson ER, Pepper AM, Marulanda G, Binitie OT, Cheong D, Letson GD. Outcome of lower-limb preservation with an expandable endoprosthesis after bone tumor resection in children. *J Bone Joint Surg Am* 2012;94(6):537–547. *This study reports the long-term follow-up of expandable prostheses.*
 13. Rao BN, Champion JE, Pratt CB, Carnesale P, Dilawari R, Fleming I, et al. Limb salvage procedures for children with osteosarcoma: an alternative to amputation. *J Pediatr Surg.* 1983;18(6):901–8.
 14. Pardasany PK, Sullivan PE, Portney LG, Mankin HJ. Advantage of limb salvage over amputation for proximal lower extremity tumors. *Clin Orthop Relat Res.* 2006;444:201–8.
 15. Nagarajan R, Neglia JP, Clohisy DR, Robison LL. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? *J Clin Oncol.* 2002;20(22):4493–501.
 16. Nagarajan R, Clohisy DR, Neglia JP, Yasui Y, Mitby PA, Sklar C, et al. Function and quality-of-life of survivors of pelvic and lower extremity osteosarcoma and Ewing's sarcoma: the Childhood Cancer Survivor Study. *Br J Cancer.* 2004;91(11):1858–65.
 17. •• Malek F, Somerson JS, Mitchel S, Williams RP. Does limb-salvage surgery offer patients better quality of life and functional capacity than amputation? *Clin Orthop Relat Res* 2012;470(7):2000–2006. *This is the most recent paper reporting functional outcomes in amputation versus limb salvage.*
 18. •• Henderson ER, Pepper AM, Letson GD. What are estimated reimbursements for lower extremity prostheses capable of surgical and nonsurgical lengthening? *Clin Orthop Relat Res* 2012;470(4):1194–1203. *Important study evaluating the economic impact of invasive versus non-invasive EPR lengthening.*
 19. Grimer RJ, Carter SR, Pynsent PB. The cost-effectiveness of limb salvage for bone tumours. *J Bone Joint Surg Br.* 1997;79(4):558–61.
 20. Harris IE, Leff AR, Gitelis S, Simon MA. Function after amputation, arthrodesis, or arthroplasty for tumors about the knee. *J Bone Joint Surg Am.* 1990;72(10):1477–85.
 21. Kawai A, Backus SI, Otis JC, Healey JH. Interrelationships of clinical outcome, length of resection, and energy cost of walking after prosthetic knee replacement following resection of a malignant tumor of the distal aspect of the femur. *J Bone Joint Surg Am.* 1998;80(6):822–31.
 22. Otis JC, Lane JM, Kroll MA. Energy cost during gait in osteosarcoma patients after resection and knee replacement and after above-the-knee amputation. *J Bone Joint Surg Am.* 1985;67(4):606–11.
 23. •• Bekkering WP, Vliet Vlieland TP, Koopman HM, Schaap GR, Bart Schreuder HW, Beishuizen A, et al. Functional ability and physical activity in children and young adults after limb-salvage or ablative surgery for lower extremity bone tumors. *J Surg Oncol* 2011;103(3):276–282. *Large series evaluating functional outcome in amputation and limb salvage.*
 24. Gottsauer-Wolf F, Kotz R, Knahr K, Kristen H, Ritschl P, Salzer M. Rotationplasty for limb salvage in the treatment of malignant tumors at the knee. A follow-up study of seventy patients. *J Bone Joint Surg Am.* 1991;73(9):1365–75.
 25. Hanlon M, Krajchich JJ. Rotationplasty in skeletally immature patients. Long-term follow-up results. *Clin Orthop Relat Res* 1999;(358):75–82.
 26. Krajchich JJ. Modified Van Nes rotationplasty in the treatment of malignant neoplasms in the lower extremities of children. *Clin Orthop Relat Res* 1991;(262):74–77.
 27. Kotz R. Tumor endoprosthesis in malignant bone tumors. *Orthopade.* 1993;22(3):160–6.
 28. Kawai A, Healey JH, Boland PJ, Athanasian EA, Jeon DG. A rotating-hinge knee replacement for malignant tumors of the femur and tibia. *J Arthroplasty.* 1999;14(2):187–96.
 29. •• Coathup MJ, Batta V, Pollock RC, Aston WJ, Cannon SR, Skinner JA, et al. 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;95(17):1569–1575. *This study demonstrates histologic evidence of bony ingrowth into an HA collar and reviews the outcomes associated with its use.*
 30. Jeys LM, Kulkarni A, Grimer RJ, Carter SR, Tillman RM, Abudu A. Endoprosthetic reconstruction for the treatment of musculoskeletal tumors of the appendicular skeleton and pelvis. *J Bone Joint Surg Am.* 2008;90(6):1265–71.
 31. • Schwartz AJ, Kabo JM, Eilber FC, Eilber FR, Eckardt JJ. Cemented distal femoral endoprostheses for musculoskeletal tumor: improved survival of modular versus custom implants. *Clin Orthop Relat Res.* 2010;468(8):2198–210. *This article reviews the outcomes of 186 cemented distal femoral EPRs, both custom and modern modular implants.*
 32. • Schwartz AJ, Kabo JM, Eilber FC, Eilber FR, Eckardt JJ. Cemented endoprosthetic reconstruction of the proximal tibia: how long do they last? *Clin Orthop Relat Res.* 2010;468(11):2875–84. *This article reviews the outcomes of cemented proximal tibial EPRs, and shows improved outcomes in modern modular implants as compared to older custom designs.*
 33. Wu CC, Henshaw RM, Pritsch T, Squires MH, Malawer MM. Implant design and resection length affect cemented endoprosthesis survival in proximal tibial reconstruction. *J Arthroplasty.* 2008;23(6):886–93.

34. Chao EY, Fuchs B, Rowland CM, Ilstrup DM, Pritchard DJ, Sim FH. Long-term results of segmental prosthesis fixation by extracortical bone-bridging and ingrowth. *J Bone Joint Surg Am*. 2004;86-A(5):948–55.
35. • Saran N, Zhang R, Turcotte RE. Osteogenic protein-1 delivered by hydroxyapatite-coated implants improves bone ingrowth in extra-cortical bone bridging. *Clin Orthop Relat Res* 2011;469(5):1470–1478. *This study demonstrates better bony ingrowth with an HA collar and synthetic bone grafting in an animal model.*
36. Kaste SC, Neel MD, Meyer WH, Pratt CB, Rao BN. Extracortical bridging callus after limb salvage surgery about the knee. *Clin Orthop Relat Res* 1999;(363):180–185.
37. Chao EY, Sim FH. Composite fixation of segmental bone/joint defect replacement (SDR) prostheses. Biological and biomechanical justifications. *Chir Organi Mov*. 1990;75(1 Suppl):171–3.
38. Tanzer M, Turcotte R, Harvey E, Bobyn JD. Extracortical bone bridging in tumor endoprostheses. Radiographic and histologic analysis. *J Bone Joint Surg Am*. 2003;85-A(12):2365–70.
39. Wunder JS, Leitch K, Griffin AM, Davis AM, Bell RS. Comparison of two methods of reconstruction for primary malignant tumors at the knee: a sequential cohort study. *J Surg Oncol* 2001;77(2):89–99. discussion 100.
40. Flint MN, Griffin AM, Bell RS, Ferguson PC, Wunder JS. Aseptic loosening is uncommon with uncemented proximal tibia tumor prostheses. *Clin Orthop Relat Res*. 2006;450:52–9.
41. Griffin AM, Parsons JA, Davis AM, Bell RS, Wunder JS. Uncemented tumor endoprostheses at the knee: root causes of failure. *Clin Orthop Relat Res*. 2005;438:71–9.
42. Farfalli GL, Boland PJ, Morris CD, Athanasian EA, Healey JH. Early equivalence of uncemented press-fit and Compress femoral fixation. *Clin Orthop Relat Res*. 2009;467(11):2792–9.
43. • Pedtke AC, Wustrack RL, Fang AS, Grimer RJ, O'Donnell RJ. Aseptic failure: how does the compress(R) implant compare to cemented stems? *Clin Orthop Relat Res* 2012;470(3):735–742. *This is a case-control study of Compress versus uncemented EPR.*
44. Bhangu AA, Kramer MJ, Grimer RJ, O'Donnell RJ. Early distal femoral endoprosthetic survival: cemented stems versus the Compress implant. *Int Orthop*. 2006;30(6):465–72.
45. Eckardt JJ, Matthews JG, 2nd, Eilber FR. Endoprosthetic reconstruction after bone tumor resections of the proximal tibia. *Orthop Clin North Am* 1991;22(1):149–160.
46. Orlic D, Smerdelj M, Kolundzic R, Bergovec M. Lower limb salvage surgery: modular endoprosthesis in bone tumour treatment. *Int Orthop*. 2006;30(6):458–64.
47. Gosheger G, Gebert C, Ahrens H, Streithuenger A, Winkelmann W, Harges J. Endoprosthetic reconstruction in 250 patients with sarcoma. *Clin Orthop Relat Res*. 2006;450:164–71.
48. Chandrasekar CR, Grimer RJ, Carter SR, Tillman RM, Abudu AT. Modular endoprosthetic replacement for metastatic tumours of the proximal femur. *J Orthop Surg Res* 2008;3:50. doi:10.1186/1749-799X-3-50.
49. Freedman EL, Eckardt JJ. A modular endoprosthetic system for tumor and non-tumor reconstruction: preliminary experience. *Orthopedics*. 1997;20(1):27–36.
50. Scales J, Sneath R. The extending prosthesis. In: Coombs R, Friedlaender G, editors. *Bone tumour management*. London: Butterworth-Heinemann; 1987. p. 168–77.
51. • Mavrogenis AF, Angelini A, Pala E, Sakellariou VI, Ruggieri P, Papagelopoulos PJ. Reconstruction of the extensor mechanism after major knee resection. *Orthopedics* 2012;35(5):e672–80. *This articles reviews techniques for extensor mechanism reconstruction.*
52. Unwin PS, Walker PS. Extendible endoprostheses for the skeletally immature. *Clin Orthop Relat Res* 1996;(322):179–193.
53. Eckardt JJ, Kabo JM, Kelley CM, Ward WG S, Asavamongkolkul A, Wirganowicz PZ, et al. Expandable endoprosthesis reconstruction in skeletally immature patients with tumors. *Clin Orthop Relat Res* 2000;373(373):51–61.
54. Cool WP, Carter SR, Grimer RJ, Tillman RM, Walker PS. Growth after extendible endoprosthetic replacement of the distal femur. *J Bone Joint Surg Br*. 1997;79(6):938–42.
55. Gupta A, Meswania J, Pollock R, Cannon SR, Briggs TW, Taylor S, et al. Non-invasive distal femoral expandable endoprosthesis for limb-salvage surgery in paediatric tumours. *J Bone Joint Surg Br*. 2006;88(5):649–54.
56. • Ruggieri P, Mavrogenis AF, Pala E, Romantini M, Manfrini M, Mercuri M. Outcome of expandable prostheses in children. *J Pediatr Orthop* 2013;33(3):244–253. *Comparative analysis of the Kotz versus Repiphysis growing EPR, showing better outcomes with the Kotz EPR.*
57. • Saghieh S, Abboud MR, Muwakkit SA, Saab R, Rao B, Haidar R. Seven-year experience of using Repiphysis expandable prosthesis in children with bone tumors. *Pediatr Blood Cancer*. 2010;55(3):457–63. *Review of 17 Repiphysis prostheses about the knee showing good MSTs scores despite a high rate of complications.*
58. • Maheshwari AV, Bergin PF, Henshaw RM. Modes of failure of custom expandable repiphysis prostheses: a report of three cases. *J Bone Joint Surg Am* 2011 6;93(13):e72. *This study discusses the poor outcomes seen in the Repiphysis implant.*
59. Beebe K, Song KJ, Ross E, Tuy B, Patterson F, Benevenia J. Functional outcomes after limb-salvage surgery and endoprosthetic reconstruction with an expandable prosthesis: a report of 4 cases. *Arch Phys Med Rehabil*. 2009;90(6):1039–47.
60. Beebe KS, Uglialoro AD, Patel N, Benevenia J, Patterson FR. Mechanical failure of the Repiphysis expandable prosthesis: a case report. *J Bone Joint Surg Am*. 2010;92(5):1250–3.
61. • Picardo NE, Blunn GW, Shekter AS, Meswania J, Aston WJ, Pollock RC, et al. The medium-term results of the Stanmore non-invasive extendible endoprosthesis in the treatment of paediatric bone tumours. *J Bone Joint Surg Br* 2012;94(3):425–430. *This study is a large series with medium follow-up of modern Stanmore non-invasive growing EPRs.*
62. • Hwang N, Grimer RJ, Carter SR, Tillman RM, Abudu A, Jeys LM. Early results of a non-invasive extendible prosthesis for limb-salvage surgery in children with bone tumours. *J Bone Joint Surg Br* 2012;94(2):265–269. *This study is a series with early to medium follow-up of modern Stanmore non-invasive growing EPRs, showing a high rate of infection despite the non-invasive growing mechanism.*
63. • Henderson ER, Groundland JS, Pala E, Dennis JA, Wooten R, Cheong D, et al. 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):418–429. *This is an important, large multicentre study identifying and classifying failure modes in EPRs.*
64. Futani H, Minamizaki T, Nishimoto Y, Abe S, Yabe H, Ueda T. Long-term follow-up after limb salvage in skeletally immature children with a primary malignant tumor of the distal end of the femur. *J Bone Joint Surg Am*. 2006;88(3):595–603.
65. • Cho WH, Song WS, Jeon DG, Kong CB, Kim JI, Lee SY. Cause of infection in proximal tibial endoprosthetic reconstructions. *Arch Orthop Trauma Surg* 2012;132(2):163–169. *Study reviewing predictors for infection in this subgroup.*
66. • Morii T, Yabe H, Morioka H, Beppu Y, Chuman H, Kawai A, et al. Postoperative deep infection in tumor endoprosthesis reconstruction around the knee. *J Orthop Sci*. 2010;15(3):331–9. *Multicenter, retrospective study documenting risk factors for infection in EPRs about the knee.*

67. •• Morii T, Morioka H, Ueda T, Araki N, Hashimoto N, Kawai A, et al. Deep infection in tumor endoprosthesis around the knee: a multi-institutional study by the Japanese musculoskeletal oncology group. *BMC Musculoskelet Disord* 2013;14:51-2474-14-51. *Large multicentre review of outcomes in infected EPRs.*
68. •• Mavrogenis AF, Pala E, Angelini A, Ferraro A, Ruggieri P. Proximal tibial resections and reconstructions: clinical outcome of 225 patients. *J Surg Oncol* 2013;107(4):335-342. *This study is a very large series with long-term follow-up of proximal tibial resections and EPR.*
69. Jeys L, Grimer R. The long-term risks of infection and amputation with limb salvage surgery using endoprostheses. *Recent Results Cancer Res.* 2009;179:75-84.
70. Jeys LM, Grimer RJ, Carter SR, Tillman RM. Risk of amputation following limb salvage surgery with endoprosthetic replacement, in a consecutive series of 1261 patients. *Int Orthop.* 2003;27(3):160-3.
71. •• Harges J, von Eiff C, Streitbuerger A, Balke M, Budny T, Henrichs MP, et al. Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. *J Surg Oncol.* 2010;101(5):389-95. *Medium term results of silver-coated EPRs showing a trend toward risk reduction in rates of infection.*
72. Dubousset J, Missenard G, Kalifa C. Management of osteogenic sarcoma in children and adolescents. *Clin Orthop Relat Res* 1991;(270):52-59.
73. • Trieb K, Goggel M, Durr HR. Proximal tibial reconstruction with gastrocnemius flap. *Oper Orthop Traumatol* 2012;24(3):263-269. *This study discusses the technique and outcomes associated with proximal tibial reconstruction.*
74. • Wang TY, Dormans JP, Chang B. Soft-tissue optimization of limb salvage with knee endoprosthesis: the 10-year experience at the Children's Hospital of Philadelphia. *Ann Plast Surg* 2012;69(5):560-564. *Study demonstrating excellent function and reduced infection risk with medial gastric flaps and EPRs about the knee.*
75. •• Hasan K, Racano A, Deheshi B, Farrokhyar F, Wunder J, Ferguson P, et al. Prophylactic antibiotic regimens in tumor surgery (PARITY) survey. *BMC Musculoskelet Disord* 2012;13:91-2474-13-91. *Study demonstrating the variation in antibiotic prophylaxis regimens in musculoskeletal oncology and the need for a randomized trial.*
76. •• Hussmann B, Johann I, Kautner MD, Landgraeber S, Jager M, Lendemann S. Measurement of the silver ion concentration in wound fluids after implantation of silver-coated megaprostheses: correlation with the clinical outcome. *Biomed Res Int* 2013;2013:763096. *This study demonstrates early reduction in inflammatory markers with silver-coated prostheses.*
77. • Gordon O, Vig Slenters T, Brunetto PS, Villaruz AE, Sturdevant DE, Otto M, et al. Silver coordination polymers for prevention of implant infection: thiol interaction, impact on respiratory chain enzymes, and hydroxyl radical induction. *Antimicrob Agents Chemother.* 2010;54(10):4208-18. *Report documenting the global metabolic effects of silver coating.*
78. Gosheger G, Harges J, Ahrens H, Streitbuerger A, Buerger H, Erren M, et al. Silver-coated megaendoprostheses in a rabbit model—an analysis of the infection rate and toxicological side effects. *Biomaterials.* 2004;25(24):5547-56.
79. •• Glehr M, Leithner A, Friesenbichler J, Goessler W, Avian A, Andreou D, et al. Argyria following the use of silver-coated megaprostheses: no association between the development of local argyria and elevated silver levels. *Bone Joint J* 2013;95B(7):988-992. *This study shows a high proportion of localized argyria in silver-coated EPR.*
80. • Shirai T, Shimizu T, Ohtani K, Zen Y, Takaya M, Tsuchiya H. Antibacterial iodine-supported titanium implants. *Acta Biomater* 2011;7(4):1928-1933. *This study provides the background evidence for iodine-coated implants in reducing infection risk.*
81. •• Tsuchiya H, Shirai T, Nishida H, Murakami H, Kabata T, Yamamoto N, et al. Innovative antimicrobial coating of titanium implants with iodine. *J Orthop Sci* 2012;17(5):595-604. *This study is a large, but heterogeneous series showing excellent outcomes with iodine-coated implants in trauma, arthroplasty and oncology settings.*
82. •• Pala E, Henderson ER, Calabro T, Angelini A, Abati CN, Trovarelli G, et al. Survival of current production tumor endoprostheses: Complications, functional results, and a comparative statistical analysis. *J Surg Oncol* 2013;108(6):403-8. *This study reviews the literature and discusses functional outcomes in the EPRs.*
83. Eckardt JJ, Lesavoy MA, Dubrow TJ, Wackym PA. Exposed endoprosthesis. Management protocol using muscle and myocutaneous flap coverage. *Clin Orthop Relat Res* 1990;251(251):220-229.
84. • Qadir I, Umer M, Baloch N. Functional outcome of limb salvage surgery with mega-endoprosthetic reconstruction for bone tumors. *Arch Orthop Trauma Surg* 2012;132(9):1227-1232. *Small series reviewing outcomes of EPRs.*
85. • Krishnamoorthy VP, Inja DB, Roy AC. Knee extensor loss and proximal tibial soft tissue defect managed successfully with simultaneous medial gastrocnemius flap, saphenous fasciocutaneous flap and medial hemisoleus flap: a case report. *J Med Case Rep* 2013;7(1):76-1947-76. *Case report discussing options for soft tissue coverage in proximal tibial EPRs.*
86. • Jentzsch T, Erschbamer M, Seeli F, Fuchs B. Extensor function after medial gastrocnemius flap reconstruction of the proximal tibia. *Clin Orthop Relat Res* 2013;471(7):2333-2339. *One of the few studies evaluating patellar height, extensor function and functional outcome in this patient population.*
87. Schwab JH, Agarwal P, Boland PJ, Kennedy JG, Healey JH. Patellar complications following distal femoral replacement after bone tumor resection. *J Bone Joint Surg Am.* 2006;88(10):2225-30.
88. Tsuboyama T, Windhager R, Campanacci D, Galletti S, Catani F, Capanna R, et al. Patellar resurfacing in tumor endoprosthesis: a study in regard to power transmission. *Chir Organi Mov.* 1994;79(3):243-50.
89. • Okita Y, Tatematsu N, Nagai K, Nakayama T, Nakamata T, Okamoto T, et al. Compensation by nonoperated joints in the lower limbs during walking after endoprosthetic knee replacement following bone tumor resection. *Clin Biomech (Bristol, Avon)* 2013;28(8):898-903. *Gait analysis study showing significant stresses in the contralateral limb following EPR.*