7 The Long-Term Risks of Infection and Amputation with Limb Salvage Surgery Using Endoprostheses

Lee Jeys and Robert Grimer

Abstract Endoprostheses are now an established technique to reconstruct defects following bone tumour resection. The long-term durability of the reconstruction is excellent, with limb salvage being maintained in the long term in 91% of patients at 20 years from surgery. The main reasons for secondary amputation were locally recurrent disease and deep periprosthetic infection. Infection remains one of the biggest threats to early failure of reconstructions with endoprostheses. Most series of reconstructions show a periprosthetic infection rate of approximately 10%. Infection most frequently occurs within 12 months from the last surgical procedure; however, the risk of infection is life-long. The commonest pathogenic organism is coagulase-negative Staphylococcus. The most effective treatment for deep infection is two-stage revision, with local treatments having little chance of curing deep infection. Research is on-going into surface treatments with silver and other materials to help to reduce the infection rates.

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7.1 Introduction

Since the late 1960s, limb salvage surgery for primary bone tumours has evolved, with the use of endoprostheses (EPRs) becoming increasingly popular throughout the world. Since the routine use of neo-adjuvant chemotherapy in the 1980s, limb salvage surgery has become the standard treatment, with limb salvage rates above 90% in most major centres. As the long-term survival from primary bone tumours rose to 60%–70% at 10 years from diagnosis, the durability of reconstruction became increasingly important.

Endoprostheses have several advantages over biological reconstruction methods, being readily available in both custom-made and modular forms, initially reliable with low complication rates and allowing rapid return to full weight bearing with predicable function (normally 70% of normal). However, there have been concerns that the long-term risks of infection, locally recurrent disease, aseptic loosening and mechanical implant failure may lead to amputations due to the inability to revise the implant.

Per-Ulf Tunn (Ed.), *Treatment of Bone and Soft Tissue Sarcomas. Recent Results in Cancer Research 179*,
DOI: 10.1007/978-3-540-77960-5,

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7.2 Long-Term Limb Salvage

The goal of any reconstruction for bone tumour surgery is to maintain a functional, painless limb in the long term. Jeys et al. [1] investigated the long-term risks of amputation in a consecutive series of 1,261 patients undergoing EPRs. They identified a subsequent amputation rate of 8.9% (n=112/1,261) with the 20-year limb salvage rate being 91%. The reasons for the amputations were: control of local recurrence (n=71; 63%), infection (n=38; 34%), mechanical failure of the prosthesis (n=2; 1.8%) and persistent pain (n=1; 0.8%). It was found that local recurrence was the single biggest risk factor affecting survival of the patient's limb. The 10-year survival of the limb fell to only 43% following local recurrence of the disease, and this was statistically significant (p<=0.0001) compared to the risk of amputation in patients without local recurrence. The risk of amputation following proven infection of an endoprosthetic replacement was 19%, compared to the risk for amputation with a local recurrence which was 36%.

For each endoprosthetic replacement site, local recurrence of tumour was the commonest cause of amputation, except for tibial endoprosthetic replacements, where infection played an equal role in causing amputation. The risk of amputation was lowest in the proximal femoral endoprosthetic replacements (5.5%) and highest in the tibial endoprosthetic replacements (15.1%). It was found that the patients with tibial endoprosthetic replacements had a statistically higher risk of amputation compared to patients with endoprosthetic replacements at other sites (p=0.001).

The time to amputation ranged from 2 days to 16½ years, with a mean of 31 months. The median time to amputation was 32 months for infection and 13 months for local recurrence. The risk of amputation decreased with time, although 10% of the amputations took place more than 5 years after insertion and late amputations occurred due to both infection and local recurrence (Fig. 7.1). Importantly there were no amputations for aseptic loosening, with both of the amputations for mechanical failure being for chronic implant instability. There were very few late amputations, with only 5% (n = 5/112) occurring after 10 years from implantation.

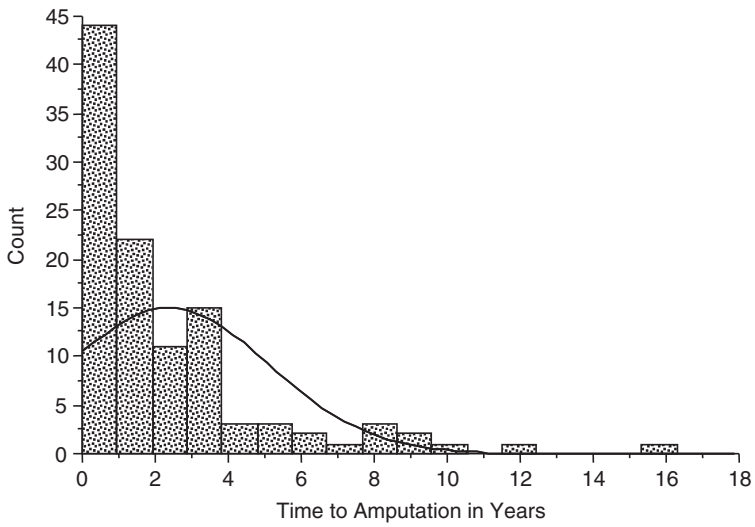

Fig. 7.1 Distribution of time to secondary amputation showing low rates of late amputations

The rate of amputation has reduced with time. Improved soft tissue cover for tibial EPRs, due to the routine use of gastrocnemius flaps, has led to significant reduction in infection rates and subsequent amputation. To date in our experience, the risk of amputation due to mechanical failure of the reconstruction with endoprostheses is negligible, with no amputations having to be performed due to aseptic loosening of implants. This suggests that reconstruction is a reliable long-term method of reconstruction.

Published results on amputation subsequent to limb salvage are quite scarce. Sim et al. [2] published a consecutive series of 50 endoprosthetic reconstructions around the knee performed between 1996 and 2005, with a mean follow-up of 2 years, with 3 subsequent amputations (6%). Sharma et al. [3] published a series of 77 distal femoral replacements performed between 1989 and 2004 with a mean follow up of 52 months. There were 5 (7%) subsequent amputations for control of local recurrence in 3 cases and infection in 2 cases. Ahlmann et al. [4] reported the outcome of endoprostheses of the lower limb in 211 patients performed between 1988 and 2003, with a mean follow-up of 14 months. There were 5 subsequent amputations (2.4%), 3 for control of infection and 2 for locally recurrent disease. Of 235 patients presenting with lower limb neoplasia, 24 (10%) underwent primary amputation. The literature is even more sparse when it comes to published limb salvage rates for new presentations of tumours, as units that have higher primary amputation rates theoretically should have less locally recurrent disease, and therefore lower secondary amputations.

Biological reconstructions are not immune to subsequent amputation. Futani et al. [5] compared endoprosthetic reconstruction to biological reconstruction for 40 skeletally immature patients with tumours of the distal femur. They found that 5 amputations were required, 1 for a skip metastasis and 4 secondarily to complications. The amputation was required in 1 of the 28 patients with an endoprosthesis (4%) compared to 3 of the 12 patients with a biological reconstruction (25%). Brigman et al. [6] reported the outcome of 116 patients under the age of 18 years who had undergone resection of a bone tumour about the knee and reconstruction with allograft. Amputation was required in 14 patients (12%), with a further 27% of patients having had a fracture and 34% having a non-union.

With modern surgical techniques and imaging, adjuvant therapy limb salvage is possible in the vast majority of patients presenting with a bone sarcoma. Endoprosthetic replacement has excellent long-term limb salvage results, despite increasing time-dependant complications. Infection and local recurrence remain the main threats to limb salvage.

7.3 Infection and Endoprostheses

Infection poses the largest iatrogenic risk to limb salvage, and controlling infection remains one the greatest challenges facing the limb salvage surgeon. Infection has always been the nemesis of orthopaedic implant surgery; however, infection rates in primary lower limb arthroplasty are currently low, typically reported to be 0.5%–2%, attributed to the use antibiotic loaded cement, antibiotic prophylaxis and clean air laminar flow theatres.

Infection of an implant is difficult to eradicate because of the adherent colonies of bacteria in a polysaccharide matrix, collectively called a biofilm [7]. This mode of growth has been implicated in a range of infections of medical devices, its importance in infection of orthopaedic implants being first noted by Gristina and Costerton [8]. Bacteria within biofilms are resistant to several hundred times the bactericidal concentrations of standard antibiotics [9]. The exact mechanism of resistance is not fully known, but hypotheses vary from protective effects of the enveloping polysaccharide to phenotypic variation

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of bacteria [10]. Infecting bacteria can remain dormant on the surface of an implant for a variable length of time. When conditions are right, clinical symptoms can be caused directly or indirectly by the local proliferation of bacteria shed by the biofilm. This may occur acutely, such as after fixation of a fracture, or several months or years after joint replacement when septic loosening occurs.

In a recent series of 1,254 patients receiving endoprostheses for musculoskeletal oncology, deep periprosthetic infection was identified in 136 (10.8%) patients [12]. The commonest pathogenic organisms were coagulase-negative Staphylococcus in 65 cultures (37%), *Staphylococcus aureus* in 35 cultures (20%), group D Streptococci in 16 cultures (9%) and *Escherichia coli* in 10 cultures (6%). These organisms are similar to ones found in published results for primary arthroplasty [13, 14]; multi-antibiotic resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Staphylococcus epidermis (VRSE) were only isolated in 5 patients.

The risk of infection varied dramatically with the site of the endoprosthetic replacement with the highest risk in the tibia at 23% (n = 57/247), pelvis 22.9% (n=11/48), distal femur 9.3% (n=48/519) and proximal femur 6% (n=18/270), and were lowest in the humerus at 1.1% (n=2/180). Infection rates have decreased with time, with infection rates since 1995 being 2.7%.

Infection typically presented within 12 months from the last surgical procedure and at a mean of 2 years from insertion of the EPR. In keeping with research from Greidanus [11], the inflammatory markers of erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were often significantly raised at presentation (mean ESR=74, mean CRP=96 mg/l).

A number of host and surgical factors were identified as the presumed cause of infection; however, it was most commonly attributed to peri-operative bacteraemia attributed to indwelling central venous lines in 11% (n=15) and revision surgery in 10.3% (n=14). Preventable causes of deep infection, such as dental sepsis, ingrowing toenails and peri-operative throat infections, have previously accounted for 15.7% of infections. All patients prior to EPR surgery are now seen by a dentist and thoroughly examined for signs of infection pre-operatively and surgery is deferred until the patient's neutrophil count is above 1,200/mm^3.

Prophylaxis against infection is clearly important and the evidence on prophylaxis with antibiotic best practice is mixed. The standard prophylaxis in our unit for a primary EPR is a 1.5 g IV bolus of cefuroxime at induction followed by 3 post-operative doses of 750 mg cefuroxime in the 24 h following surgery. For revision surgery we favour a glycopeptide at induction, which continues for 5 days post-operatively until the results from samples taken at surgery are available. Antibiotic prophylaxis for patients with EPRs undergoing dental treatment is equally contentious. Guidelines from the British Orthopaedic Association for patients with total joint replacement is that no antibiotic prophylaxis is required; however, our advice to patients undergoing invasive procedures that risk bacteraemia is that they should have prophylaxis with amoxicillin (1 g IV or 3 g orally), which is the recommended regimen for patients with artificial heart valves.

Treatment for infection is arduous, time-consuming and expensive. The best treatment regime has been debated for primary arthroplasty, with both one-stage and two-stage revision having their advocates [16–19]. In our published series for EPRs [12], two-stage revision (n=58), amputation (n=43), surgical debridement (n=41), one-stage revision (n=33), coverage with a soft tissue flap (n=15), antibiotic impregnated beads (n=11), antibiotic impregnated cement (n=7), excision arthroplasty (n=2) and arthrodesis (n=1) were all attempted. Local treatments, such as surgical debridement (2.4%; n=1/41), arthroscopic washout (7.7%; n=1/13), antibiotics alone

(6.8%; $n=8/117$) or impregnated beads/cement (11.1%; $n=2/18$) have little chance of curing deep infection. The limb salvage treatment with the best probability of curing deep infection was two-stage revision (70.7%, $n=41/58$), which was significantly more effective than one-stage revision (42.4%, Fig. 7.2). In our unit this entails removing the infected prosthesis with a thorough debridement of all the pseudocapsule (including the scar tissue behind the knee), inserting an antibiotic-impregnated cement spacer for a minimum of 7 weeks with parenteral antibiotics matched to the sensitivity of the isolated organism (Fig. 7.3). A new prosthesis can then be inserted if an aspirate taken from the peri-prosthetic cavity 4 weeks after the first stage revision (with no antibiotics for 1 week prior to aspiration) fails to grow any organism on extended cultures after 3 weeks. Multiple tissue samples are taken at the second stage of revision and the patient is kept on treatment antibiotics until the cultures are negative after 5 days incubation. If deep tissue samples are positive, intravenous antibiotics are continued for 6 weeks post-operatively.

Patients who have a deep infection have a significantly ($p<0.001$) higher risk of amputation (36.7%) compared with those without infection (6.2%); however, following the routine use of two-stage revision, the rate of amputation has reduced to approximately 25% for infections.

Several risk factors were identified that significantly increased the risk of deep infection and these were radiation therapy, subsequent patellar resurfacing, extendable prostheses, a tibial EPR site, a pelvic EPR site and subsequent operation to replace polythene bushings.

Recent published infection rates for tumour prostheses are similar to our results. Sharma et al. [3], published a series of 77 distal femoral EPRs with a mean follow-up of 52 months, with 6 deep infections (7.8%). Flint et al. [21] described a series of 44 uncemented proximal tibial EPRs with 7 deep infections (15.9%). Gosheger et al. [22] described one the largest series of 250 EPRs with a deep infection occurring in 30 patients (12%).

Infection is also a problem in biological reconstruction, in a series of 25 vascularized

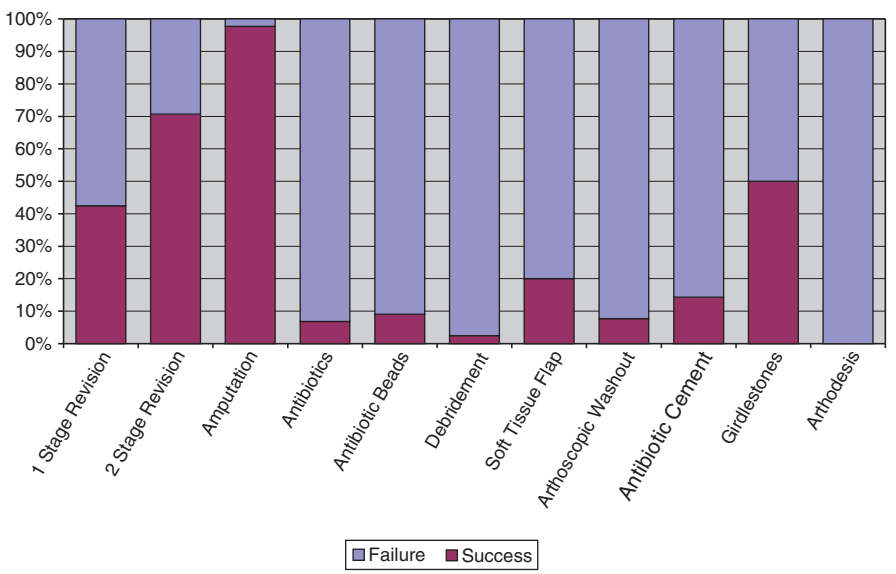

Fig. 7.2 Efficacy of treatments employed to deal with deep infection

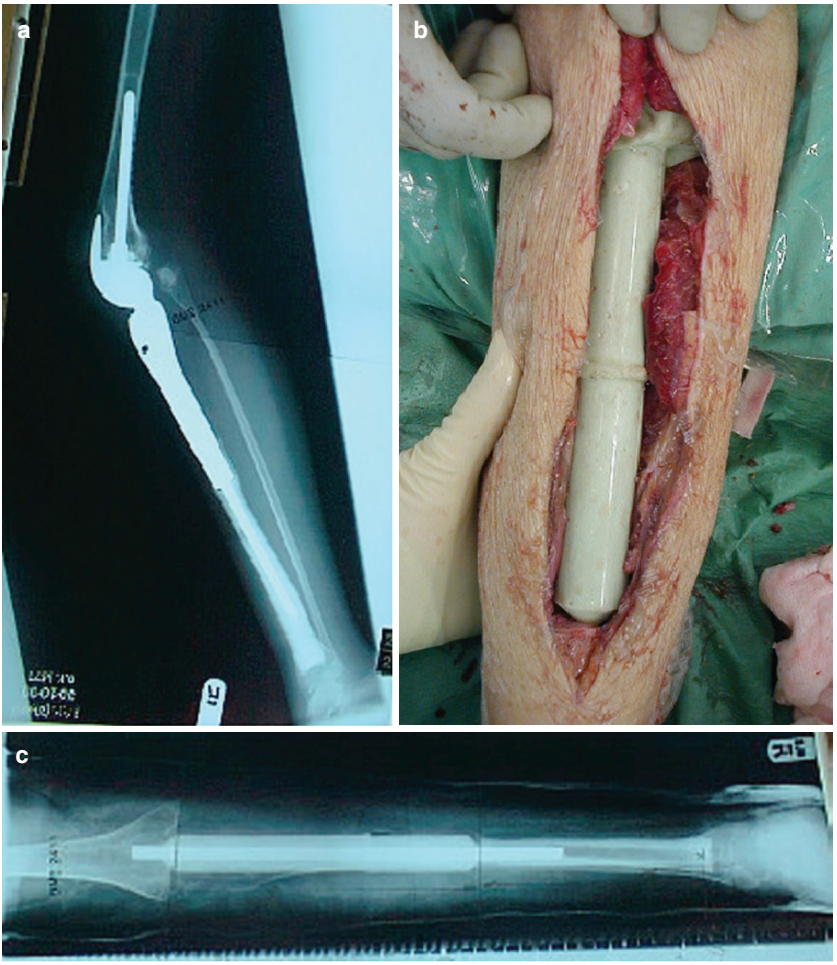

Fig. 7.3 **a** Radiograph of chronic infection in EPR. **b** Clinical photograph and **c** radiograph of cement space in situ

fibula strut grafts, Chen et al. [23], described 3 infections (12%). Muscolo et al. [24] described their experience of osteoarticular allografts of the distal femur; of the 62 patients available for review, 6 reconstructions failed due to infection (9.7%). Brigman et al. [6] showed a 16% infection rate in their series of 116 patients under the age of 18 years treated with allografts around the knee.

Some encouraging research from both animal [25, 26] and human studies [27] has shown that for patients with osteosarcoma, deep infection may have a survival benefit. In patients who had a deep early infection without metastases at presentation, the 10-year survival rate of 84.5% in the infected group compared to 62.2% in the non-infected group ($p=0.017$; Fig. 7.4). Deep infection had no effect on the development of

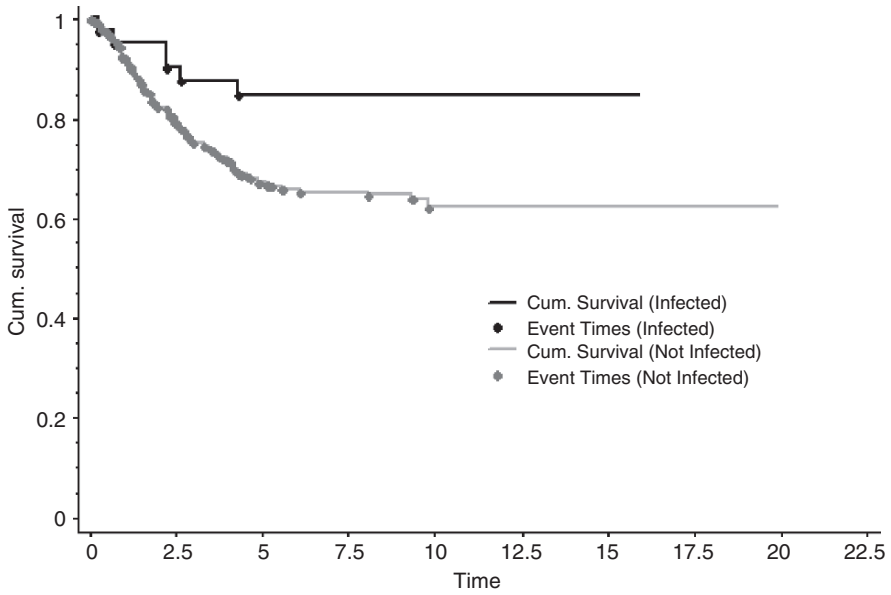

Fig. 7.4 Kaplan–Meier survival curves of survival rates for osteosarcoma for patients with and without deep infection using landmark analysis

locally recurrent disease ($p=0.56$) or distant metastases ($p=0.29$). There was a trend towards an increased time to metastases in the infected group but this was not significant ($p=0.09$, mean time for infected group = 85 months, mean time for non-infected group = 64 months). The postulated mechanisms for increased survival included stimulation of tumour necrosis factor (TNF)-α, cytotoxic cell-mediated tumour suppression and prevention of tumour neovascularization.

7.4 New Techniques to Combat Infection

With all types of reconstruction suffering similar significant levels of failure due to infection, the research efforts of several groups have identified ways that infection may be reduced, with the majority of emphasis being placed on prevention of infection rather than treatment.

7.4.1 Surface Treatments

Various chemicals are either bactericidal or bacteriostatic and considerable research is ongoing into how these could be incorporated into implants. The greatest interest is directed towards the coating of implants with silver. The anti-bacterial properties of silver have been known for thousands of years, dating back to ancient Greece. Silver, in its ionic form, binds to bacterial DNA, hindering bacterial replication and simultaneous deactivation of metabolic enzymes. Silver surface coatings have been used in a variety of medical devices from urinary catheters to cardiac valves. The sustained slow release of silver nanoparticles may prove to be important in the long-term effectiveness of this technology. Gosheger et al. [28, 29] have shown that silver coating of EPRs can reduce the infection rate in animal models and is non-toxic in humans. Other surface materials

such as bioactive ceramics, antibiotic derivatives and surfactants to disrupt biofilms have all been investigated [30–33]. Antibiotics may be loaded into morcelized and allograft bone grafts in an attempt to reduce infection, and iontophoresis may be a novel technique to ensure high tissue levels of antibiotics in the perioperative period [34–36].

7.4.2 Antibiotic Prophylaxis

The bacteria implicated in peri-prosthetic infection has evolved from *Staphylococcus aureus* through coagulase-negative Staphylococcus to the emerging threat of multi-drug resistant organisms. Al-Maiyah et al. [37] showed that 9% of surgical gloves were contaminated during surgery, most frequently with coagulase-negative Staphylococcus, and that the majority of isolates were not sensitive to cefuroxime. This finding has been replicated when studying the organisms isolated at revision surgery for infection. Several authors have suggested that glycopeptides should be used in the routine prophylaxis of joint replacements, though the evidence for this is limited [38–41].

7.5 Conclusions

Limb salvage surgery with endoprostheses is established and has shown good long-term results, comparable with biological reconstructions. Amputation, on the other hand, poses a significant long-term risk, often due to locally recurrent disease or deep periprosthetic sepsis. Infection rates are widely reported to be approximately 10%, with treatment being arduous and time-consuming. In our experience, two-stage revision surgeries have the best chance of limb salvage with acceptable results. Technological advances, including surface coatings, may help to reduce the risk of infection.

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