EDITORIAL

INFECTION FOLLOWING BONE TUMOR RESECTION AND RECONSTRUCTION WITH TUMORAL PROSTHESES: A LITERATURE REVIEW

C. GRACI, G. MACCAURO, F. MURATORI[1], M.S. SPINELLI, M.A.ROSA[2] and C. FABBRICIANI

Orthopaedic Institute, Catholic Univerisity of Rome; [1]Orthopaedic Department, Azienda Ospedaliera Reggio Emilia; [2]Orthopaedic Department, University of Messina, Italy

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Bone resection is the choice treatment of malignant bone tumors. Tumor prosthesis is one of the most common solutions of reconstruction following resection of bone tumor located to the metaphysis of long bones. Periprosthetic infections are a frequent complication of limb-salvage surgery which is largely due to prolonged and repeated surgeries, as well as to the immunocompromised condition of these patients due to neoplastic treatment. Furthermore, the large exposure of tissues during this type of surgery and the dissection across vascular distributions also contributes to the high risk of infection. The authors reviewed the literature discussing the incidence of infections of tumor prosthesis implanted following resection of bone tumors, taking into account the different sites of implantation. In the English literature, the highest risk of infection which led to limb amputation was observed after proximal tibia resection and this difference was considered to be due to the poor condition of soft tissue and also after pelvic resection due to huge dead space after sarcoma resection not filled by implant. Independent of the location, the management of infected prosthesis is similar. That is, after one or more attempts at debridement and antibiotic therapy, it consists of implant removal and insertion of a new implant in a one- or two-stage procedure, with a decreased risk of failure with the two-stage procedure.

After wide tumor resection, limb-salvage procedures are considered the treatment of choice in 85-95% of cases (1), in comparison to the past when the surgical option was most frequently limb amputation. Limb reconstruction is usually obtained by tumor prostheses and the evolution of these implants has significantly modified clinical outcomes of limb bone tumors.

Currently, in many centres, limb salvage surgery and reconstruction with endoprosthesis is considered the standard procedure for treatment of malignant bone tumors located in metaphysis of long bones. This is due to the improvement in operative techniques, better patient selection and advances in prosthetic designs. Nowadays, the use of this procedure is markedly increased in the treatment of both aggressive benign and malignant musculoskeletal neoplasms. The advantages of prosthetic reconstruction include rapid functional restoration as well as good long- term functional outcome. The disadvantages include the risk of wear, aseptic loosening, fracture and peri-prosthetic infection (2-3).

The implantation of a prosthesis presents several complications. One of the most feared is undoubtedly

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Mailing address: Giulio Maccauro MD,
Orthopaedic Institute,
Catholic University of Rome,
Largo F. Vito 1,
00168 Rome, Italy
Tel: ++39 06 30154353 Fax: ++39 06 3051161
e-mail: giuliomac@tiscali.it

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infection which is sometimes more feared than local recurrence itself. Malnutrition, hyperglycemia, long duration of surgery, chemotherapy, multiple previous operations, irradiated soft tissue and local soft tissue condition are all well-known risk factors for infection. It is recommended that before implantation of arthroplasty, septic foci (skin, dental, urinary infections, etc.) detection and removal should be carried out, in accordance with the patient's condition. Frequently, neoplastic patients are immunocompromised and malnourished with a decreased healing capability and, theoretically, an increased risk of deep prosthetic infection (4-5). The infection rates vary in different anatomical districts which is probably due to difference of muscle coverage of the implant (6).

A deep infection exposes the patient to many risks including repeated surgical interventions, a longer rehabilitation period, pain, possibly poorer functional outcome, and in the worst case scenario, even amputation (2, 7).

There are many classifications of peri-prosthetic infections found in the literature. One of the most common, which we used in this study, is that of McPherson et al. (8) which consists of 3 types:

Type I: early postoperative infection (< 4 postoperative weeks);

Type II: acute hematogenous infection;

Type III: late chronic infection (> 4 postoperative weeks).

The infection rate reported in different series ranges from 8% to 15% (9-10), even if some authors reported an infection rate from 0 to 33% (11). Capanna reported an infection rate of 43% in cases of revision surgery in tumor endoprosthesis, independently on implant site (3).

In the literature, many centres reported their experience in the management of infections following tumor resection and reconstruction with tumoral prosthesis and they showed different modalities of management.

The aim of this study is to report an overview of the incidence of infections in tumoral prosthesis in different areas and the possible surgical options available in terms of management of such cases.

PROXIMAL FEMUR

The proximal femoral metaphysis is the most common segment involved in bone tumor, and femoral resection and reconstruction with modular endoprosthesis is one of the most commonly used treatments. This technique allows for wide margin surgery combined with a good functional recovery. However, endoprosthesis replacement has its own complications such as dislocation, peri-prosthetic infections and aseptic loosening.

In our experience, from 1993 to 2003, we reported 23 cases of proximal femur bone resections and reconstructions with modular prosthesis. Neoadjuvant chemotherapy was used for responding tumors, such as osteosarcoma. Bone resection and reconstruction in cases of bone metastasis was restricted to young patients with good life expectancy, carcinomas with good prognosis, such as breast or thyroid cancers, patients with solitary bone metastasis without parenchymatous involvement at the time of surgery, or bone metastases in patients with carcinoma who are non-responsive to adjuvant therapy (e.g., renal carcinoma).

Antibiotic therapy with a third-generation cephalosporin was administered two hours before surgery and five days postoperatively. Deep infection was observed in two patients treated with irrigation, debridement and intravenous antibiotic therapy (12).

Deep infection was the most common surgical complication reported in a study by Jacofsky. He reported four deep infections in a series of 42 patients treated with hip arthroplasty to salvage failed treatment (either established non-union or acute hardware failure) of a malignant pathologic proximal femur fracture. Three patients underwent resection arthroplasty and one underwent debridement as well as one stage re-implantation. One of these patients required multiple operations and ultimately hip disarticulation for the control of sepsis. He was undertaking chemotherapy treatment and had received previous irradiation for metastatic lung carcinoma (13).

Sokolovski et al. reported six cases (13.6%) of late infection in a series of 44 patients. Four of these cases (9.1%) were treated conservatively with antibiotics while in the other two (4.5%), a revision endoprosthesis hip replacement was performed. *Staphylococcus aureus* was the most common pathogen identified. The results were excellent after treatment, with no recurrence of infection (14).

Farid et al. compared the results of two consecutive series of patients with either segmental endoprosthetic replacement or allograft-prosthetic composite reconstruction to evaluate complications, functional scores, and construct survival. In 52 patients with endoprostheses, two cases (4%) of deep infection were observed. In one case of early infection, after four wound irrigation and debridement procedures failed, the patient was treated with implant removal and no reconstruction. Another case described was a patient with late infection (36 months post-operatively), after three wound debridement procedures and a prolonged course of intravenous antibiotics, the infection was eradicated without implant removal. Limb function was restored to the pre-infection level. Of the 20 patients with allograft-prosthetic composite reconstructions, one patient (5%) had a late infection developed 89 months post-operatively and was treated with implant removal and prosthetic revision (15).

KNEE

The distal femur and proximal tibia are common anatomic locations for primary and metastatic bone tumors. Limb-salvage surgery has replaced amputation as the treatment of choice for distal femur primary tumors. This method offers considerable advantages in terms of function, cosmetic appearance and psychological acceptance. It is generally considered to be cost-effective if compared with amputation (16).

Infection around the knee after major tumor reconstruction surgery is a common problem in 10 to 20% of patients. Amputation is required in 37% to 87% of patients (6, 17).

Manoso et al. reported a series of eleven patients treated between 1990-2001 with an infected knee reconstruction following cancer limb-salvage surgery. The initial neoplastic lesion was located in the distal femur in 8 patients and in the proximal tibia in the remaining 3. The average time from the primary surgery to the development of infection was about 6 months. Five patients had failed prior surgical debridements in an attempt to eradicate the infection. The most common pathogen was *Staphylococcus aureus* (6 patients), the second one was *Staphylococcus epidermidis* (3 patients). All patients were treated with staged reconstruction protocol. Staged debridement and free tissue transfer was indicated in areas with inadequate soft tissue to cover the re-implanted prosthesis. The protocol consisted of initial prosthetic removal and implantation of an antibiotic-impregnated cement spacer. Patients were treated with iv antibiotics for a minimum of 6 weeks post-operatively. Six patients were treated with a single antibiotic, while the other 5 patients were treated with multi-drug regimes for multi-microbial infections. A second debridement and spacer change was performed following the completion of the iv antibiotic regimes. The average number of debridement procedures was 3. The patients underwent delayed prosthetic reconstruction and free tissue transfer only when intra-operative and/or aspiration cultures were negative after the termination of antibiotics. All limbs were saved without any amputation or flap loss. Ten patients (91%) remained free of recurrent infection while for 1 patient, the protocol failed to eradicate the infection (16).

In 110 consecutive patients, Bickels reported six deep infections (5.4%) resulting in three amputations, two prosthetic revisions and one wound debridement (17).

Myers et al. reported 32 deep infection cases in a series of 192 distal femur replacements after an average period of 13 months. Early amputation was needed for seven patients, while the other 25 cases had a two-stage revision in an attempt to control the infection. This was successful in 17 but failed in eight cases which were then treated with a late amputation. No difference was found in terms of infectioun risk between the fixed-hinge and rotating-hinge endoprostheses (18).

Hardes et al. emphasized that patients with poor local soft tissue conditions frequently located at the proximal tibia have a high risk for secondary amputation (19). Jeys at al. also found that the risk for secondary amputation due to infection was highest with proximal tibial replacements (6).

PROXIMAL HUMERUS

The proximal humerus is one of the primary sites of tumors. Amputation of the upper limb is very mutilating and artificial limbs provide limited function and poor cosmetic appearance. For these reasons limb-preserving techniques were established soon after the introduction of adjuvant treatment. Survivability after large segment proximal humerus endoprostheses is excellent, especially when compared with the use of large segmental prostheses at other anatomic sites such as the distal femur and proximal tibia.

Wittig et al. reported 100% prosthetic survival rate of 15 patients in an average follow-up period of 10 years without infections. Furthermore, the use of local muscular rotational flaps has reduced the complications, especially of late infections. Sometimes the pectoralis major flap is used in soft tissue covering of the entire prosthesis (20).

ELBOW

The distal humerus is rarely affected by bone tumors. In fact, only 1% of primary bone tumors arise in the distal humerus. Endoprosthetic replacement may be used to reconstruct the elbow and distal humerus after tumor resection. The advantages are immediate stability and early functional recovery, while the potential disadvantages include the likelihood of implant failure due to either wear, loosening, infection or fracture. The poor soft tissue coverage at the elbow could increase the infection rate.

Ross et al. described four neoplastic patients who had distal humerus endoprosthesis as a part of a series of distal and total humeral replacement for a variety of causes. The rates of local recurrence, infection and aseptic loosening were all 11.5% at short term follow-up (21). Kulkarni et al., in a series of 1,743 primary bone tumors, described 17 located in the distal humerus. Of these 17 cases, 10 underwent endoprosthetic replacement of the distal humerus and no infection was observed after prosthetic reconstruction (22).

PELVIS

In pelvic sarcoma, the external hemipelvectomy was the primary choice of surgical intervention. With the introduction of aggressive chemotherapy, improvement in imaging studies and more advanced surgical techniques, limb-sparing resections have been carried out for primary malignancies of the pelvis. The resection of the tumor should be followed by a reliable and functional reconstruction with minimal morbidity. Current options for surgical reconstruction also include custom-made endoprosthesis combined with hip arthroplasty or the modular saddle prosthesis. Infection remains a frequent complication of internal hemipelvectomy with reported rates varying from 12 to 47% (23).

Aljassir et al. reported 10 infections in a retrospective review of 27 patients. Four cases had superficial wound infections that only required wound irrigation, debridement and intravenous antibiotics. The other six had deep infections. Of these, four had infected haematomas that responded to debridement and irrigation; one infection ended with chronic drainage and one patient required implant removal and ended with massive heterotopic ossification that gave the patient a stable pseudoarthrosis. Most infections were observed in chondrosarcoma despite the absence of adjuvant treatment. The high rate of infectious complications could be attributed to the creation of a huge dead space after sarcoma resection (which cannot be filled by the implant) and also to the long duration of the surgical procedure (24).

SURGICAL MANAGEMENT

Several studies demonstrated a very low rate of deep infection eradication with the use of local treatment alone (local surgical debridement, arthroscopic washout and use of antibiotics or antibiotic-laden beads or cement) (6, 25).

One-stage procedure consists of the removal of all the components as well as accurate debridement of necrotic and infected tissue and immediate implant of the new prosthesis. This procedure has several advantages including: it is a single operation, it preserves functional movement and the integrity of soft tissue, and it is low cost. Care should be taken in revisions around the knee because of scar tissue close to the popliteal vessels and nerves.

Two-stage procedure is considered by many authors the gold-standard for infection eradication. It consists of implant removal and antibiotic-loaded cement spacer insertion, followed later by implant of a new prosthesis. The most commonly added

Table I. *Review of the literature according to infection rate.*

Study	N. patients	Site of tumor	N. infections	Infection rate (%)
Rosa et al. [28]	23	Proximal femur	2	8.7
Jacofsky et al. [29]	42	Proximal femur	4	9.5
Sokolovski et al. [30]	44	Proximal femur	6	13.6
Farid et al. [31]	72	Proximal femur	3	4.1
Jeys et al. [22]	270	Proximal femur	18	6.7
Myers et al [42]	192	Knee	32	16.6
Bickels et al. [36]	110	Knee	6	5.4
Jeys et al. [22]	712	Knee	105	14.7
Aljassir et al. [41]	27	Pelvis	10	37

antibiotic is vancomycin due to the high sensibility of staphylococcus species. Intravenous antibiotics are changeable according to the sensitivities of the organisms obtained from the cultures. The wound is checked at 3 weeks and the spacer cavity aspirated to ensure the absence of any residual infection. If these cultures are positive, then the systemic antibiotics should be changed or the spacer should be removed and replaced with a new one incorporating the appropriate antibiotics.

Holzer et al. reported a series of 18 patients treated by one-stage revision surgery without removing the intramedullary stem. Patients were followed with a mean period of 52 months. Success was observed in 14 cases (26). This one-stage revision surgery in infected hip replacement was disliked by Crockarell et al. who found that after 6 years of follow-up, the success rate had fallen to 14% compared with an optimistic figure of over 80% after 6 months (27).

Hanssen and Rand reviewed the treatment of different infected hip and knee arthroplasty. They reported a 60% success rate with one stage revision surgery without antibiotic-loaded cement; 83% success with one-stage revision surgery with antibiotic-loaded cement; 82% success with two-stage revision surgery without antibiotic-loaded cement and 90% success with two-stage revision surgery with antibiotic-loaded cement (28).

Hanssen et al. concluded that two-stage revision surgery has a slightly higher success rate than one-stage revision surgery. At the second stage the wound is re-opened and the fluid is sent for culture. The spacer and surrounded pseudo-capsule are removed. The intramedullary canal is cleaned and all granulation tissue is removed. The new endoprosthesis is inserted and the wound is closed, leaving a surgical drain. Intravenous antibiotics are again continued until the culture results (taken at the time of the operation) become available (29).

Grimer et al. from 1989 to 1998 treated 34 infected endoprosthesis cases by two-stage revision surgery. Of these, 24 had the infection completely controlled from the time of the operation, with a follow-up ranging from 6 to 116 months. Recurrence of the infection occurred in three patients who had undergone previous treatment with radiotherapy. Six patients required amputation for persistent infection, three for early failures and the other three for late failures (11).

DISCUSSION

Infection most frequently occurs within 12 months from the last surgical procedure however, the risk of infection is life-long (30). The incidence of infection following bone tumor resection and reconstruction with tumoral prosthesis is significantly higher than that after conventional joint replacement which in some case studies ranges from 0 to 33% (11).

Infection of tumor prosthesis may lead to major morbidity and sometimes amputation. Oncologic patients have a high risk of infection due to neoadjuvant chemotherapy, long duration of surgery and extensive exposure during the surgery itself. The highest infection rate has been observed in proximal tibia, pelvis, and in children who had frequent lengthening procedures.

The diagnosis of infection is obtained when the results of cultures taken at the time of revision surgery are positive, when VES and reactive C protein are positive and when there are clinical features present suggesting an infected prosthesis. Acute polymicrobial infection and the administration of chemo and radiation therapy are associated with a higher risk of limb salvage failure, leading to early amputation in some patients (11).

Re-implantation should be avoided during adjuvant chemotherapy because of the higher risk of recurrent infection in immunocompromised patients. Successful re-implantation of a prosthesis should only be performed in the presence of sufficient soft tissue coverage.

Insufficient muscle coverage of the prosthesis can be improved by a vascularized muscle transfer or a free muscle flap transfer. Although the use of a muscle flap is not sufficient in all cases to restore the soft tissue defect caused by the tumor resection and tissue damage due to the infection itself. Limb salvage can sometimes be achieved by performing an arthrodesis during which adequate muscle coverage is usually easier to obtain.

The treatment of patients with tumor prosthesis infection is often challenging and time-consuming, requiring a high number of operations. This long-standing treatment should be performed only if there is a good chance for limb salvage. In some cases, repeated operations and intravenous antibiotic treatment are unable to eradicate these infections so that secondary amputation or hip disarticulation remain the only available solutions.

Late low-grade infection can be treated initially with intravenous antibiotics. In the case of rising inflammatory parameters, implant removal and cement spacer implantation should be considered. Debridement with prosthesis retention and one-stage re-implantation without the changing of intramedullary stem can be successful in the case of early infection. In cases of late high-grade infection, one-stage revision surgery is not recommended.

The two-stage revision is the best limb-salvage procedure for eradicating a deep infection. This procedure includes the removal of the prosthesis and the positioning of antibiotic-impregnated cement spacer which should remain in place for a minimum of six weeks (25, 31). The next stage can be performed only if no organisms grow after three weeks from cultures of periprosthetic aspirate (6).

Jeys et al. reported 136 infections out of 1,264 patients treated with oncological prosthesis. They reported an infection rate of 11.8 %. In 127 patients, the infection was identified by isolation of an organism on microbiological culture, whereas the remaining nine patients had clinical and histological evidence of infection at the time of revision surgery. The specimen for culture was obtained by aspiration of fluid from the periprosthetic cavity in 91 patients. Intra-operative specimens were gained from 14 patients, and wound swabs were obtained from 22 patients. The most common pathogenic organism was coagulase-negative Staphylococcus which was identified in 65 patients (48%). Multiple organisms were isolated in 36 patients (26%) with the most common combination being coagulase-negative Staphylococcus and group-D streptococcus. The presence of multiple organisms does not reduce the success rate of treatment of infection or the rate of acceptable functional results post- surgery (6).

In recent years, the use of silver-coated prosthesis has spread to reduce the infection rate due to reduction of bacterial proliferation in presence of silver-coated titanium implants compared to titanium alone. In one study, Hardes et al. investigated the infection rate in patients with titanium tumor prostheses compared with patients who were implanted with silver-coated prostheses. They showed that the infection rate in patients with silver-coated titanium implants was 5.9% versus 17.6% in patients with titanium implants (32-33). To date, there are few studies in the literature that demonstrate absolute antimicrobial efficacy of silver or the absence of possible local or systemic toxicological side-effects related to the use of silver (34).

Deep infection had no impact on the development of locally recurrent disease or distant metastases. However, in a study by Jeys et al. it was observed that in infected patients, the time period without metastases was longer but this was not significant. The postulated mechanisms for increased survival included stimulation of tumor necrosis factor (TNF)-α, cytotoxic cell-mediated tumor suppression and prevention of tumor neovascularization (35).

CONCLUSION

Infection is one of the most serious complications after prosthetic reconstruction procedure in limb salvage surgery. The incidence of infection after tumor resection is high. This is because of several factors including the long duration of surgery, the repeated operations performed and the immunocompromised conditions of the patients as a result of neo-adjuvent therapy. In addition, the large exposure of tissues during these operations and the dissection across vascular distributions contributes to the high incidence of infection. Frequently, in these oncological orthopaedic procedures, an additional flap surgery to maintain adequate soft tissue coverage is necessary to prevent infection.

This complication requires surgeons to remove implants, or even to amputate the limb. The knee joint is the main site of infection due to poor soft tissue coverage. Coagulase-negative Staphylococcus is the pathogenic organism most often identified. The polymicrobial infection is associated with a higher risk of limb salvage failure.

Debridement with prosthesis retention and one stage re-implantation can be successful in the case of an early infection. However, in most cases, the two stage revision represents the gold-standard treatment to eradicate a periprosthetic infection.

The prophylactic measures that can reduce infection are clean air laminar flow environment, double preparation of the patient's skin with alcohol-based solutions, adhesive skin dressing and preoperative intravenous dose of broad spectrum cephalosporin.

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