Management of septic complications following modular endoprosthetic reconstruction of the proximal femur

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Abstract In a retrospective single-centre study 170 consecutive patients were included who received a Kotz modular prosthesis after resection of bone tumours of the proximal femur to evaluate the management of prosthetic infection. Infection occurred in 12 of 166 patients available for follow-up (six males; six females; mean age, 47 years; range, ten to 75 years) after a mean of 39 months (range, one to 166 months; infection rate, 7.2%). Mean follow-up was 54 months (range, four to 200 months). One patient died of septic shock. Two patients were treated by wound revision only. Treatment of infection in the remaining patients was one-stage revision in eight and hip disarticulation in one. Infection control by one-stage revision was achieved in five of eight patients; re-infection occurred in three patients and was successfully treated by further revision in all of them. The overall success rate for controlling infection was 83.3%.

Introduction

The proximal femur is a common site for primary bone tumours and the most common site for metastatic lesions apart from the axial skeleton [1]. Due to advances in adjuvant therapy, surgical technique and modular prosthetic design, limb salvage surgery today is the standard treatment for patients with musculoskeletal malignancies [2–6], especially around the hip [7–10]. Despite these advances,

however, there are still major potential complications including infection, aseptic loosening, implant fracture and dislocation [4–12]. The most serious complication in this context remains deep infection, with rates ranging between 8% and 14% [4, 7–10, 13–15]. The potentially higher risk of infection in megaprotheses for treatment of bone and soft tissue cancer compared to conventional joint arthroplasty may be related to longer operating times, soft tissue dissection and immunosuppression [2, 4, 11, 12]. A deep infection exposes the patient to the risks of repeated surgical procedures, long rehabilitation, pain, loss of limb function and amputation [2, 4, 8, 13, 16, 17]. Excision arthroplasty or arthrodesis is no viable solution due to the amount of bone removed at the time of the initial tumour resection. The options for controlling infection include debridement, lavage, irrigation, and one- or two-stage revision [18–24]. In infected total hip arthroplasty (THA) one- and two-stage revision has the best results [18–24]. However, little published data is available concerning modular prostheses and is mostly confined to small clinical series. Furthermore, there have been no reports, to date, focussing exclusively on the management of deep infection of proximal femur prostheses.

The aim of this study was to investigate the risk of deep prosthetic infection, the predisposing factors, and the success of subsequent treatment in patients with deep infection of modular tumour prostheses of the proximal femur for bone and soft tissue cancer, presenting the largest single-centre study on modular proximal femur prostheses.

Material and methods

A retrospective cohort study was performed using prospectively collected data from the Vienna Bone and Soft Tissue

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Tumour Registry. We identified 170 consecutive patients who underwent limb salvage for a tumour around the proximal femur using a modular endoprosthetic reconstruction between June 1982 and September 2008. Four patients (2.4%) were excluded from the study because of inadequate follow-up. The study design and protocol were approved by the respective institutional review board.

There were 81 males and 85 females available for follow-up with a mean age of 49.8 ± 20.1 years (range, 5.9–84.3 years) at the time of operation. Seventy-one patients (42.8%) had a primary malignant tumour, eight (4.8%) had either myeloma or lymphoma, one (0.6%) had eosinophilic granuloma, and 86 (51.8%) underwent resection for metastatic disease. At the time of this review, 112 patients (67.5%) had died of their oncological disease. The overall mean follow-up was 47 ± 67 months (range, 0–365 months). Ninety-one patients received neoadjuvant chemotherapy, 73 received local radiotherapy and 44 received both. The KMFTR (Kotz Modular Femur and Tibia Reconstruction System, Howmedica GmbH, Kiel, Germany) and HMRS (Howmedica Modular Reconstruction System, Howmedica GmbH, Kiel, Germany) have been used since 1982 to reconstruct large segmental defects. More recently, the GMRS (Global Modular Reconstruction System, Stryker Corp., Mahwah, NJ) has been implanted ($N=21$; Fig. 1). Twelve patients required cemented fixation with a gentamycin-loaded bone cement (Palacos®R+G; Heraeus Medical, Hanau, Germany) for metaphyseal anchorage of the stem, and all other 158 patients had cementless fixation of their prosthesis. A cemented acetabular component was used in 14 patients with tumour involvement of the acetabulum.

Patients were considered to have a deep infection when they had clinical evidence of infection with a positive microbiological culture or periprosthetic pus and histological evidence of infection at the time of revision. Infections were classified according to the system of Coventry and Fitzgerald et al. [25, 26]. Accordingly, a class-I infection presents within four weeks after operation, a class-II between four weeks and two years after the operation and class-III, more than two years after the operation.

One-stage revision involved removal of all exchangeable components and all polyethylene parts with exception of the anchorage components. In addition, all infected surrounding soft tissues, as well as the periprosthetic scar tissue sleeve were thoroughly debrided. Povidone iodine (Betaisodona®; Mundipharma, Limburg/Lahn, Germany) was used to rinse the wound and pack it with povidone iodine sponges before a provisional closure. Thereafter, the area of surgery was disinfected again, the patient redraped and the entire operating team changed gowns and gloves. After reopening the wound with new instruments and removal of the sponges,

another thorough rinsing and cleaning of the wound and the anchorage components were performed before implantation of new prosthetic components.

In contrast to one-stage revision, in a two-staged treatment the entire prosthesis was removed, including anchorage components. After thorough soft tissue debridement a cement spacer was produced inside a cement gun with Kuntscher nails inside to provide adequate strength. A gentamycin-loaded bone cement (Palacos®R+G; Heraeus Medical, Hanau, Germany) additionally enriched with vancomycin was used for all spacers. Appropriate antibiotics were added depending on the sensitivity of the isolated organism, whenever available, at the time of operation. At three weeks the spacer cavity aspirated to ensure absence of any residual infection. If these cultures proved positive then the systemic antibiotics were changed. In all patients, a sterile aspirate was achieved before proceeding to secondary implantation. The second procedure was performed between one and seven months after explantation.

Successful eradication of infection was defined as the absence of clinical signs of sepsis and inflammation for at least six months by means of local surgical revision. Amputation was not regarded as successful local control of infection.

Statistical analysis

Descriptive data (mean, standard deviation, range) were reported for the entire patient cohort. Significant differences in means were calculated with the *t*-test. Cross-tabulation was performed with Fisher's exact test. Tests of independence were calculated with the chi-squared test. Survival analysis was performed according to the Kaplan-Meier method. Differences in survival were calculated by log-rank testing. The investigated endpoint was prosthetic infection as defined above. A *p*-value of or below 0.05 was regarded significant. Data was analysed using GraphPad Prism® software (GraphPad Software Inc., LaJolla, CA).

Results

The overall survival without infection was 95.9% at one year, 89.2% at five years, 89.2% at ten years, and 77.8% at 20 years (Fig. 2). Deep infection occurred in 12 of 166 patients (7.2%) after a mean of 39 ± 60 months (range, 0–167 months, Table 1). There were six male and six female patients with a mean age of 47.2 ± 21.4 years (range, 9.6–75.3 years) at the time of endoprosthetic reconstruction. Their histological diagnoses were chondrosarcoma (five patients), osteosarcoma (two), liposarcoma (two), and leiomyosarcoma and eosinophilic granuloma (one each).

Fig. 1 Radiological example of a 47-year-old male patient with a grade 2 chondrosarcoma of the left proximal femur. Pre-operative radiographs (a, b), pre-operative MRI (c) and postoperative radio-

graphs (d, e) after wide tumour resection and reconstruction with a modular GMRS prosthesis and a bipolar head

The remaining patient was treated for metastatic breast cancer. The mean follow-up period from the time of infection was 54 ± 60 months (range, 0–201 months). Three patients required cemented fixation and four patients had additional pelvic reconstruction. Six patients received chemotherapy, five had radiation therapy and three had both. The infection rate has slightly decreased over the last ten years (1999–2008) of the study period (4.9%, compared to 8.6% for the years before 1999). The mean time from insertion of the prosthesis to infection was 39 ± 60 months (range, 0–167 months), whereas the mean time from the last revision to infection was 6 ± 7 months (range, 0–18 months). Seven patients (58.3%) suffered from infection within two years (median, five months) after insertion of the prosthesis,

Fig. 2 Kaplan-Meier estimation of cumulative infection-free survival of 166 patients with modular prosthetic reconstruction of the proximal femur

and all patients presented within two years after the last surgical procedure, suggesting that revision surgery was a predisposing factor for subsequent infection.

The pathogenic agents were identified by microbiological cultures in ten patients (83.3%), whereas the remaining two patients had clinical and/or histological evidence of infection at revision surgery. The most common causative organisms were *Coagulase-negative staphylococcus* and *Staphylococcus epidermidis* (three patients each). In four patients (30.8%), multiple organisms were isolated. According to the system of Coventry and Fitzgerald [25, 26], there were two class-I infections, five class-II infections, and five class-III infections (Table 1).

There was a significantly ($p < 0.01$) increased rate of infection (15.3%) in those patients treated for primary tumours ($n = 72$) versus those treated for metastatic disease ($n = 94$; 1.1%) (Fig. 3). Patients with cemented ($n = 12$) prosthesis had a significantly ($p < 0.05$) higher risk of infection compared to those with uncemented ($n = 154$) prosthesis (25.0% versus 5.8%). Patients with additional pelvic reconstruction ($n = 14$) had an infection rate of 42.8%, which was significantly ($p < 0.0001$) higher than in patients with reconstruction of the proximal femur alone ($n = 152$; 3.9%; Fig. 4). Patients who did not undergo radiotherapy or subsequently required revision ($n = 104$) presented an infection rate of 3.9%, which was lower than in patients who had radiotherapy or additional operation ($n = 62$; 12.9%); however, this was not significant.

Infection was treated by local revision in ten of the 12 patients (Table 2). One patient (case 5) died due to general sepsis on the fourth postoperative day. Another patient (case 4) with postoperative skin breakdown underwent

Table 1 Clinical details of patients with deep infection associated with modular prostheses of the proximal femur

Case	Age (y)	Gender	Diagnosis	Cement	Acetabular component	Time to infection (mo)	Cause of infection	Infecting organisms	Infection classification	Follow-up (mo)
1	55	Male	Chondro sarcoma	–	–	0	Sepsis	Negative	Type I	0
2	60	Female	Metastasis	+	–	1	Wound dehiscence	<i>Klebsiella pneumoniae</i> , <i>Proteus vulgaris</i>	Type I	10
3	21	Male	Chondro sarcoma	–	–	1	Wound dehiscence	<i>vancomycinresistent Enterococcus faecalis</i>	Type II	30
4	60	Male	Leiomyo sarcoma	+	–	3	Poor tissue mantle	<i>Coag-neg. staphylococci</i>	Type II	7
5	10	Female	Osteosarcoma	–	–	4	Unknown	<i>Coag-neg. staphylococci</i>	Type II	11
6	75	Female	Chondro sarcoma	–	+	9	Wound dehiscence	<i>Staphylococcus epidermidis</i>	Type II	41
7	26	Male	Chondro sarcoma	–	+	14	Unknown	<i>Staphylococcus aureus</i>	Type II	37
8	63	Male	Chondro sarcoma	+	+	30	Poor tissue mantle	<i>Staphylococcus epidermidis</i> , <i>Campylobacter</i>	Type III	124
9	54	Female	Eosinophilic Granuloma	–	+	32	After revision	Negative	Type III	109
10	58	Male	Liposarcoma	–	–	49	After revision	<i>Staphylococcus aureus</i>	Type III	250
11	39	Female	Liposarcoma	–	–	158	After revision	<i>Staphylococcus epidermidis</i>	Type III	365
12	17	Female	Osteosarcoma	–	+	167	After revision	<i>Coag-neg. staphylococci</i> , <i>Enterococcus faecalis</i>	Type III	225

revision by a pedicled rectus abdominis muscle transposition flap and split-thickness skin graft. The soft tissue condition was poor and following two subsequent revisions for skin coverage the patient developed deep prosthetic infection and underwent amputation within three months.

Local wound revision and irrigation was successfully performed in two patients with only mild signs of infection,

whereas one of them (case 8) required hip disarticulation because of complete palsy of the sciatic nerve following three subsequent failed revisions within three years after successful infection control. The remaining eight patients were treated by one-stage revision. In six patients infection control was achieved by one-stage revision for a mean follow-up of 66 months (range, 7–201 months); five of

Fig. 3 Kaplan-Meier estimation of cumulative infection-free survival according to the type of indication. Patients treated for primary tumours had a significantly lower infection-free survival ($p < 0.05$) than patients treated for metastases

Fig. 4 Kaplan-Meier estimation of cumulative infection-free survival according to the type of reconstruction. Patients with additional pelvic reconstruction (Prox femur + Pelvis) had a significantly lower infection-free survival ($p < 0.0001$) than patients with reconstruction of the proximal femur alone (Prox femur)

Table 2 Treatment results of deep infection associated with modular prostheses of the proximal femur

Case	Chemotherapy	Radiotherapy	Revision surgery	Treatment	Initial success	Time to reinfection (mo)	Cause of reinfection	Final success	Patient survival (mo)
1	.			None	No	.	.	No	0, died
2	.			One-stage revision	Yes	.	.	Yes	9
3	.	Yes	Yes	Wound revision	Yes	.	.	Yes	20, died
4	CWSS	Yes		Hip disarticulation	No	.	.	No	4, died
5	EURA-MOS			One-stage revision	Yes	.	.	Yes	7, died
6	.			One-stage revision	Yes	.	.	Yes	32
7	.			One-stage revision	Yes	.	.	Yes	23
8	.			Wound revision	Yes	.	.	Yes	94
9	COSS	Yes	Yes	One-stage revision	Yes	.	.	Yes	77, died
10	.	Yes	Yes	One-stage revision	No	165	After revision	Yes	201, died
11	Cyvadic	Yes		One-stage revision	No	90	Unknown	Yes	119
12	COSS			One-stage revision	No	0	Poor tissue mantle	Yes	59

them remained without recurrent infection. One patient (case 11) developed re-infection seven years after the first one-stage revision. Another one-stage revision was carried out and successfully controlled the infection. The two remaining patients had two-stage revision procedures, both after previous unsuccessful one-stage revisions. One (number 12) developed infection two weeks after revision surgery. Within one month, two one-stage revisions were performed without success. Subsequently, a two-stage revision successfully eradicated the infection over the next four years. The other patient (number 10) underwent two revision operations for local recurrence and then developed infection 49 months after index surgery. One-stage revision had controlled the infection for 13 years. Then the patient suffered from re-infection and multiple recurrent dislocations of the hip. Accordingly, two-stage revision was performed, which controlled the infection for three years until the patient died from heart failure.

The overall success rate for controlling infection was 83.3% (ten of 12 patients). Re-infection occurred in three patients 0, 90 and 165 months after the first revision, respectively, and was successfully treated in all of them (Table 2). Five patients died for reasons not related to infection four to 201 months after revision. Patients who had developed deep infection had an average of 2.1 additional operations after the insertion of the original prosthesis compared with an average of 0.5 additional operations for the patients without deep infection ($p <$

0.001). The mean duration of hospital stay was 35 days (range, 5–81).

Discussion

This study exclusively presents the treatment of infection within the largest single-centre series of modular proximal femur prostheses with similar design. The overall infection control provided by mainly one-stage revision has shown a satisfactory outcome. The results were dependent on further revision, fixation technique (cemented versus uncemented), the use of acetabular components and potentially from adjuvant therapy. There certainly were limitations to this study primarily including its retrospective design. Furthermore, the number of patients with prosthetic infection was low and therefore deduction and conclusions from this population are limited, but still might be useful in defining a standardised treatment algorithm.

Deep prosthetic infection is a serious complication of any joint arthroplasty [2, 4, 13, 17]. The risk of infection in cancer patients is significantly higher than in the general arthroplasty population [7–9, 21, 27]. Malignant tumours, previous surgery, and long operating times were major risk factors for the development of infections around prosthetic joints [28]. Accordingly, the incidence of deep infection following limb salvage surgery for bone tumours is significantly higher than after conventional joint replacement

and varies from 0% in the humerus to 33% in the proximal tibia [4, 7, 13, 20, 22, 29, 30]. The problem of infection following proximal femoral replacement has been documented by several authors with infection rates ranging from 1.8% to 19.5% [7–9, 15, 27]. The rate of infection in our series was 7.3%, comparable to the incidence of 6.3% and 6% reported by Menendez et al. [9] and Chandrasekar et al. [7], respectively (Table 3). In our series, however, there was a considerably longer interval, with two patients (cases 11 and 12) not developing infection until 15 years after endoprosthetic reconstruction. Gosheger et al. [27] reported an infection rate of 19.5% in 41 patients, attributing their high infection rate to four patients who received postoperative radiotherapy after resection of Ewing's sarcoma. In fact, a study of 1,240 patients published by Jeys et al. [15] recorded that radiation therapy was a significant risk factor for infection. In our series, the infection rate in patients with primary bone tumours who underwent radiotherapy was 20% (4/20) compared to 11.8% (6/51) in the patients who did not.

The diagnosis of deep infection in our series was confirmed by positive microbiological cultures or periprosthetic pus or histological evidence obtained at the time of revision surgery. These criteria are accepted as indicators of definite infection [31]. In concordance with other published series of patients with deep infection following total joint arthroplasty, *Coagulase-negative Staphylococcus* together with *Staphylococcus epidermidis* were the most frequently isolated pathogenic organisms [32].

After deep infection in conventional total joint arthroplasty, one-stage [33, 34] or two-stage revision surgery with complete exchange of all prosthetic components and the use of antibiotic-loaded bone cement is recommended [35, 36]. Hanssen and Rand [21] reviewed the treatment of infected hip or knee arthroplasty and recorded an 83% success rate with one-stage revision and 90% success rate with two-stage revision both with antibiotic-loaded cement,

suggesting that the latter is more successful in eradication of deep infections. In oncological patients who require revision for infected megaprotheses, however, additional risk factors are related to the use of chemotherapy or radiotherapy or both and to the large bone defects and dramatically larger expanse of potentially infected areas associated with tissue necrosis. In fact, patients with infected megaprotheses definitely require a more aggressive approach for controlling infection. One-stage revision was the preferred primary option for infection control at our institution. Two patients, however, with only mild signs of infection were successfully treated with wound debridement only. The advantages of a one-stage revision procedure are the avoidance of explantation of the prosthesis and thus leaving the patient with a large bone defect, the need for only one operation and less stress for the patient, a shorter period of hospitalisation and lower costs. Additionally, it offers the comfort of continuously preserving the patient's function and mobility. This is one of the key benefits compared to two-stage revision, which leads to immobilisation of the patient for several weeks.

Holzer et al. [22] earlier reported on 18 patients with KMFTR prostheses treated by one-stage revision at our institution. The success rate was 77.8% at six months, and they observed no late recurrence of infection. The fact that in all patients infection was localised within the scar and did not track along the bone–prosthesis interface considerably contributed to their satisfactory results. In our series, infection also did not invade the medullary canal, and although we routinely performed meticulous debridement of potentially contaminated soft tissue, the overall success rate of infection control was slightly lower (62.5%). One possible explanation for the higher failure rate, however, is the fact that according to the anatomical circumstances of the hip joint thorough debridement of adjacent soft tissue is virtually impossible, compared to the knee. Grimer et al. [20] reported on 34 patients with a follow-up ranging from six to 116 months after two-stage revision surgery and successful infection control in 24 of 34 patients (70.6%). Flint et al. [19] published a series of 15 patients who were treated by two-stage revision and with a success rate of 72.7% (8/11). The prosthetic system used in this series was the same uncemented modular replacement that was used in our study, and the anchorage sections were similarly left in situ at the time of debridement. In comparison to Grimer et al. [20], the analysis of Flint et al. [19] distinguished between patients who had their diaphyseal anchorage stems retained and patients who had their original prostheses completely removed. In the latter group the rate of successful eradication of infection was lower with 40%. This was attributed to the belief that a well-ingrown stem may potentially function as a physical barrier, preventing entry of infection into the medullary canal [14, 19].

Table 3 Comparison of the infection rates of our series with other published series of modular proximal femoral reconstruction

Authors	Number of patients	Period of study	Infection rate (%)
Kabukcuoglu et al. [6] (custom)	54	1972–1992	1.8
Gosheger et al. [26] (modular)	41	1992–2003	19.5
Menendez et al. [7] (modular)	96	1992–2003	6.3
Chandrasekar et al. [5] (modular)	100	2001–2006	6.0
Present series (modular)	166	1982–2008	7.3

Re-infection developed in three patients in our series with none leading to amputation. One patient was successfully retreated by one-stage revision and the remaining two underwent successful two-stage revision. In comparison, in the series published by Grimer et al. [20], re-infection proved disastrous with four of the seven patients having an amputation and two dying from metastatic disease with an infected endoprosthesis still in situ. In view of the fact that arthrodesis or resection arthroplasty is not feasible in patients with large bone defects, the seriousness of controlling deep infection with the initial revision procedure cannot be emphasised enough. In this context Grimer et al. [20] reported an overall amputation rate of 17.7% (6/34), and Flint et al. [19] even indicate a rate of 26.7% (4/15). The rate of amputation for infection in this series was 8.3% with only one out of 12 patients requiring hip disarticulation.

Interestingly, in our series all re-infections developed in patients who had presented as class-III infections (more than two years after operation). Apart from that, late re-infections seemed to develop after additional operations on the prosthesis for causes unrelated to infection despite the use of prophylactic antibiotics and careful asepsis. It seems that surgical stimulus can act as a potent source of infection, and it is clear that both the patient and the surgeon should be aware of this risk before performing any additional surgical procedures.

Conclusion

Our results suggest that patients with antibiotic-sensitive organisms in the setting of a well-fixed uncemented modular tumour system can be managed with one-stage revision surgery without exchange of the anchorage components. Experience shows, however, that if the infection has been present for more than a few days, the prospects of infection eradication with this technique are limited. Two-stage revision surgery should be used as a salvage procedure for patients with organisms resistant to antibiotics and in case of re-infection. Furthermore, two-stage revision procedures should also be taken into consideration for patients with delayed, chronic infections and potentially loose implants.

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