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ORIGINAL ARTICLE

Cemented versus cementless endoprostheses for lower limb salvage surgery

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Summary

Purpose: *To determine the survival and failures of cemented vs cementless endoprostheses.*

Methods: *We retrospectively studied 232 patients treated with lower limb salvage surgery and reconstruction using cementless and cemented endoprostheses from 2002 to 2007. We compared survival and failures of the endoprostheses regarding age, gender, body mass index (BMI), diagnosis, site of reconstruction, radiation therapy, chemotherapy, and stem fixation.*

Results: *The mean patient follow-up was 28 months (median 24; range 12-84). The overall survival of cemented and cementless endoprostheses at 60 months was 64 and 78%, respectively (p=0.0078). Survival at 60 months of cemented and cementless endoprostheses to infection was 68 and 82%, respectively (p=0.0248). Survival of cemented and cementless endoprostheses to aseptic loosening at 60 months was 94 and 96%, respectively (p=0.1493). The only significant univariate and multivariate predictor of survival was the cementless type of stem fixation.*

Conclusion: *Cementless endoprostheses have higher overall survival and survival to infection compared to cemented endoprostheses. Survival to aseptic loosening is not different. Stem fixation is the only significant variable for survival.*

Key words: *apoptosis , Euphorbia lunulata Bge, hepatoma, HepG2 cells*

Introduction

Advances in the understanding of the biology and staging of tumors, imaging techniques, adjuvant treatments, and improvement in metallurgy of endoprostheses have enabled limb salvage surgery to be considered the treatment of choice for most tumors of the lower limb [1-5]. Reconstruction techniques following limb salvage include massive allografts or allograft-prosthetic composites [6-10], endoprostheses, rotationplasty and arthrodesis [11].

Modern designs of endoprostheses include cemented and cementless stems, modular segments, rotating hinge knee, circumferential porous coating at the bone-prosthesis interface, and options for reattachment of soft tissue such as the hip abductors and the knee extensor mechanism. Complications such as aseptic loosening [1,12-15], breakage [1,12-16], dislocation of the prosthetic joint [1,12-15], dissociation of the modular components of the prostheses [1,12], and infection [1,13,17] have been reported with both cemented and cementless endoprostheses. Cementless stems have evolved in the last 25 years and less is known about their results compared to cemented stems. Cementless fixation may be advantageous because of bone ingrowth surface that may lead to a very low aseptic loosening rate [18]. However, despite an attentive review of the literature, it remains unclear whether cementless tumor prostheses have comparable survival and complications with cemented prostheses, and there is no clear support regarding one method of fixation vs another [1,13-15].

Therefore, we performed this study of a series of patients with oncological diagnoses treated with limb salvage and reconstruction using

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Table 1. Diagnoses of the 232 patients included in this series

Diagnosis	*Cemented (124 patients) N (%)*	*Cementless (108 patients) N (%)*
Osteosarcoma	25 (20.1)	64 (59.2)
Chondrosarcoma	13 (10.5)	8 (7.4)
Malignant fibrous histiocytoma of bone	7 (5.6)	-
Ewing's sarcoma	4 (3.2)	9 (8.3)
Lymphoma	5 (4.0)	-
Myeloma	4 (3.2)	-
Spindle cell sarcoma of bone	6 (4.8)	6 (5.5)
Dedifferentiated fibrosarcoma of bone	1 (0.8)	-
Leiomyosarcoma	1 (0.8)	3 (2.7)
Soft tissue liposarcoma	1 (0.8)	-
Radiation-induced osteosarcoma	-	1 (0.9)
Bone metastases	53 (42.7)	3 (2.7)
Giant cell tumor	3 (2.4)	14 (12.9)
Cementifying fibroma (cementoma)	1 (0.8)	-

cementless and cemented endoprostheses to address the controversy regarding the use of bone cement for stem fixation of endoprosthetic reconstructions in the lower extremities. We evaluated the survival and failures of the cemented vs the cementless endoprostheses, and the effect of age, gender, BMI, diagnosis, site of reconstruction, associated radiation therapy or chemotherapy, and type of stem fixation on the survival of the endoprostheses..

Methods

We retrospectively studied the files of 232 patients with primary and metastatic tumors of the lower extremities treated with limb salvage and endoprosthetic reconstruction at the authors' institutions from January 2002 to December 2007 (Table 1). There were 122 males and 110 females with a mean age of 47 years (range 9-80). The mean follow-up was 28 months (median 24; range 12-84). Twelve patients were lost to follow-up. The mean follow-up for the cemented prostheses was 28 months (median 24; range 12-89), and the mean follow-up for the cementless prostheses was 44 months (median 40; range 20-78). All patients gave written informed consent to be included in this study which was approved by the Institutional Review Board/ Ethics Committee of the authors' institutions.

Patients were staged using the surgical staging system of the Musculoskeletal Tumor Society (MSTS) system [19]; sarcoma patients had all stages of intra- or extra-compartmental tumors; patients with bone metastases had solitary bone lesions with bone destruction and impending or actual pathological fracture, favorable tumor histology such as breast and thyroid cancer, and long expected survival; patients with benign tumor had stage 3 lesions. All patients were administered prophylaxis with intravenous antibiotics including teicoplanin and amikacin for 5 days; in children, a second generation cephalosporin was administered for the same time period. As documented by intraoperative frozen sections and postoperative histological examination of the resected tumor specimens, wide resection was achieved in 214 (92.2%) patients and marginal resection in 18 (7.8%). In all patients with bone metastases, wide en bloc resection was performed. Reconstruction following resection was done using an MRS® or a GMRS® endoprosthesis (Stryker-Howmedica Inc, Rutherford, NJ). These endoprostheses are part of the same modular prosthetic system. They incorporate a rotating hinge knee mechanism and titanium or chromium-cobalt-molybdenum, straight-fluted, cemented or cementless stems with hydroxyapatite coating; the

Table 2. Sites of reconstruction and types of stem fixation

Site	*Cemented (124 cases) N (%)*	*Cementless (108 cases) N (%)*
Distal femur	49 (39.5)	69 (63.8)
Proximal femur	48 (38.7)	10 (9.2)
Proximal tibia	17 (13.7)	28 (25.9)
Total femur	9 (7.2)	1 (0.9)
Distal femur and proximal tibia	1 (0.8)	–

knee hinge is the same in both prostheses. MRS® is available only with cemented stems, while GMRS® is available with cemented and cementless stems; cemented fixation was done in 124 (53.4%) cases and cementless in 108 (46.6%) cases (Table 2). Candidates for cemented fixation were patients with bone metastases and extensive osteolytic defects such as hemoproliferative lesions. Candidates for cementless fixation were younger patients and patients with primary bone tumors. Cement technique was the same in all patients; we used third generation cement technique with vacuum mix and centrifugation for cement preparation, canal preparation with brushing lavage, and insertion of the cement under pressure with a cement gun. In 32 of the 46 (69.9%) patients with proximal tibia resections and reconstructions, wound coverage and reattachment of the extensor mechanism of the knee was done using the medial gastrocnemius muscle flap; in the remaining cases, direct attachment of the extensor mechanism and wound closure was performed. In all patients with proximal femoral resections and reconstructions, soft-tissue reconstruction of the hip abductors was done by suturing the tendons to the remaining host soft-tissue without direct reattachment to the endoprosthesis.

Perioperative adjuvant treatments were administered according to the primary tumors' histology. Radiation therapy alone was administered in 48 patients with cemented endoprostheses and in 2 with cementless endoprostheses. Chemotherapy alone was administered to 74 patients with cemented endoprostheses and 76 with cementless endoprostheses. Combined radiation therapy and chemotherapy was administered in 29 patients with cemented endoprostheses and in 2 patients with cementless endoprostheses. In all patients, postoperative management included bed rest and analgesics, and weight-bearing as tolerated using a walker or crutches after the second postoperative day, aiming to mobilize the patients as soon as possible to prevent immobilization-related complications such as deep venous thrombosis and urinary infections. In patients with hip abductor or knee extensor mechanism reconstruction, immobilization with a hinged hip or knee brace was done for 3 weeks for soft-tissue healing, and progressive range of motion and muscle strengthening exercises were started thereafter. At discharge from hospital, all patients were instructed for continuous physical therapy and assisted walking for 6 weeks, supervised by a physical therapist or a physical medicine and rehabilitation doctor.

Routine follow-up evaluation was performed every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually. Each follow-up evaluation included clinical examination and standard radiographs of the site of reconstruction; computed tomography of the chest was done annually. Complications and endoprostheses-related causes of failure were recorded. Causes of failure of the endoprostheses were considered any implant-related events such as infection, aseptic loosening and breakage that would necessitate revision of the prosthesis, or amputation. Amputation because of tumor local recurrence was not considered failure of the endoprosthesis in the implants' survival analysis. Periprosthetic infection was diagnosed by clinical examination and increased values of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell count in joint fluid analysis.

Statistics

The actuarial endoprosthesis' overall survival, and survival to infection and aseptic loosening were analyzed using the Kaplan-Meier survival analysis [20], using as starting point the date of implantation and as end point the failure of endoprosthesis. Differences in

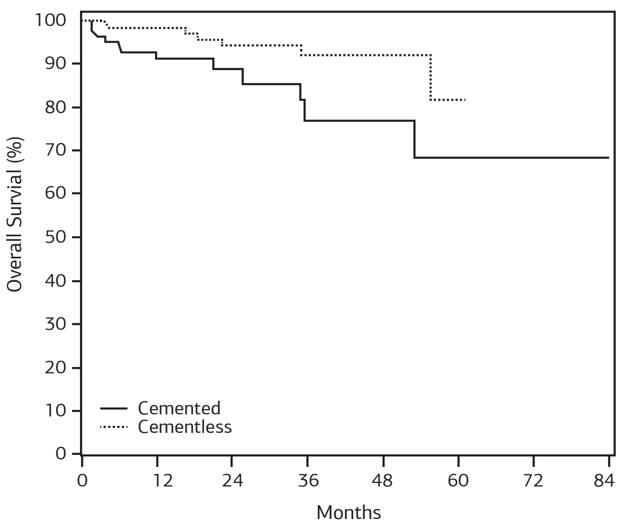

Figure 1. Overall survival to failure of the cemented and cementless endoprostheses at 60 months was 64 and 78%, respectively (p= 0.0078; 95% CI: 1.3269-6.4634).

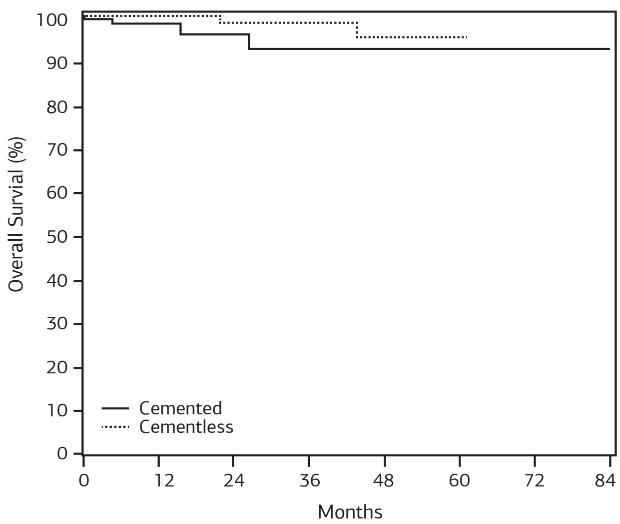

Figure 2. Survival to infection of the cemented and cementless endoprostheses at 60 months was 68 and 82%, respectively (p= 0.0248; 95% CI: 1.1395-6.8917).

Table 3. Failures and complications according to the site of reconstruction. Failure was considered any complication that would lead to revision surgery

Complications	*Overall (N= 220)* N (%)*	*Distal femur (N= 113) N (%)*	*Proximal femur (N= 53) N (%)*	*Proximal tibia (N= 44) N (%)*	*Total femur (N= 9) N (%)*	*Distal femur and proximal tibia (N= 1) N (%)*
Infection	20 (9.1)	9 (8)	4 (7.5)	5 (11.4)	2 (22)	
Aseptic loosening	7 (3.2)	2 (1.7)	2 (3.8)	3 (6.8)		
Wound dehiscence		5 (4.4)				1
Superficial wound infection		1 (0.9)	1 (0.9)			
Patellar tendon rupture				4 (9)		
Hinge block		1 (0.9)				
Patella dislocation		1 (0.9)				
Knee stiffness		1 (0.9)				
Hematoma formation		3 (2.6)			1	
Hip dislocation			2			

*Twelve of 232 patients lost to follow-up were not included in the analysis

Table 4. Univariate and multivariate predictors of survival of the endoprostheses

Variable	*Univariate analysis*	*Multivariate analysis*		
	p-value	*p-value*	*Odds ratio*	*95% CI*
Body mass index	0.6797	0.7289	1.0116	0.9479 to 1.0796
Diagnosis	0.9349	0.3565	2.0499	0.4492 to 9.3545
Age	0.5750	0.6948	0.9988	0.9928 to 1.0048
Gender	0.9466	0.5453	1.3056	0.5526 to 3.0847
Site of reconstruction	0.5225	0.6136	1.1383	0.6903 to 1.8770
Radiation therapy	0.7108	0.1727	0.3037	0.0553 to 1.6695
Chemotherapy	0.0826	0.2449	2.1468	0.5962 to 7.7295
Type of stem fixation	0.0175	0.0169	3.4236	1.2530 to 9.3544

Cementless type of stem fixation was the only univariate and multivariate predictor of survival of the endoprostheses

survival were determined with log-rank test. The effect on survival of (1) age (age of 47 years was chosen as a cutoff because it was the mean age of the patients), (2) gender, (3) BMI (BMI of 25 kg/m^2 was chosen as a cutoff because it is the limit between normal and overweight), (4) diagnosis, (5) site of reconstruction, (6) radiation therapy, (7) chemotherapy and (8) type of stem fixation was evaluated using both univariate analysis and multivariate Cox regression analysis with stepwise forward procedure [21]. The data were recorded in a Microsoft® Excel® 2003 spreadsheet (Microsoft Corporation, Redmond, WA, USA) and analyzed using MedCalc® Software Version 11.1 (MedCalc Software, Mariakerke, Belgium).

Results

Survival rates

At the last follow-up, 220 of the 232 (94.8%) endoprostheses (116 cemented and 104 cementless prostheses) were available for analysis. Twenty-seven (17 cemented and 10 cementless prostheses) of the 220 (12.3%) endoprostheses failed, and were revised because of infection (20 prostheses) and aseptic loosening (7 prostheses) (Table 3). The overall survival of the cemented endoprostheses was 64% at 60 months, while the overall survival of the cementless endoprostheses was 78% at 60 months (p=0.0078; Figure 1).

Twenty endoprostheses failed and were revised because of infection (9.1%); there were 12 cemented (10.3%) and 8 cementless (7.7%) endoprostheses. Survival of the cemented endoprostheses to infection was 68% at 60 months, while survival of the cementless endoprostheses was 82% at 60 months (p=0.0248; Figure 2). Eighteen patients with infected endoprostheses were successfully treated with two-stage revision surgery; removal of the cementless implants was easier compared to cemented implants and resulted in less bone loss that didn't complicate the reconstruction after removal of the prosthesis in any case. Instead, cement made revision for infection more difficult; chisels and drills were used and, if necessary, controlled perforation of the cortical bone or osteotomies were performed. Two patients with cemented endoprostheses underwent amputation as definitive management for infection.

Seven endoprostheses failed and were revised because of aseptic loosening (3.2%); there were 5 cemented (4.3%) and 2 cementless (1.8%) endoprostheses. Survival of the cemented endoprostheses to aseptic loosening was 94% at 60 months, while survival of the cementless endoprostheses was 96% at 60 months (p=0.1493; Figure 3). In revision for aseptic loosening, no particular difficulties were observed between cemented and cementless endoprostheses. Extraction was generally not difficult because a well-defined plane was formed at the bone-implant or bone-cement interface.

Univariate and multivariate predictors of survival

In univariate analysis, the only variable that was found to be predictor of survival was cementless type of stem fixation (p= 0.0175). A trend to significance was observed with respect to the use of chemotherapy (p= 0.0826). In multivariate analysis, cementless type of stem fixation was also the only significant variable for predicting survival (p= 0.0169); age, gender, BMI, diagnosis, site of reconstruction, radiation therapy and chemotherapy were not statistically significant predictors of the survival of endoprostheses (Table 4).

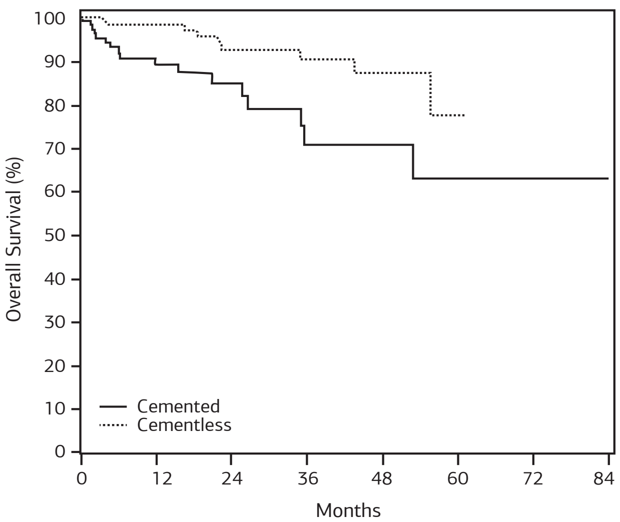

Figure 3. Survival to aseptic loosening of the cemented and cementless endoprostheses at 60 months was 94 and 96%, respectively (p= 0.1493; 95% CI: 0.6440-18.0017).

Discussion

Reconstruction after limb salvage surgery is challenging. Currently, the most widely used method of reconstruction are endoprostheses [4,13]. However, early and late implant-related complications arising from the extensive bone and soft tissue defects, technically challenging and lengthy surgical procedures, complex reconstructions, and implants' size are common [12,13,18,22]. Endoprosthetic reconstructions eventually fail and require revision [18,22]. To prevent failure and improve the survival of the endoprostheses, the choice of the implant and the use of bone cement for fixation remain unclear [1,5,11-15]. We performed this retrospective study of patients treated with limb salvage surgery and endoprosthetic reconstruction to evaluate the survival of the prostheses and the effect of age, gender, BMI, diagnosis, site of reconstruction, radiation therapy, chemotherapy, and cemented or cementless type of stem fixation on survival. Our results showed that overall survival and survival to infection was statistically significantly higher for the cementless endoprostheses. With the numbers available, the only univariate and multivariate predictor of survival of the endoprostheses was the cementless type of stem fixation. A trend for significance was observed with respect to the use of chemotherapy.

This study presents 2 major limitations. First, the retrospective design, short-term follow-up and inclusion of patients with various primary diagnoses, reconstruction sites and adjuvants are important limitations. However, we opted to include all patients with lower limb salvage and reconstruction to increase the sample size and strengthen our results, and to draw important conclusions regarding the use or not of bone cement for oncological lower limb salvage reconstructions. We included patients with total femoral replacement to evaluate cement fixation at the tibia in patients with extensive bone and soft tissue defects. We also included patients with metastatic bone disease to evaluate the survival of the endoprostheses and the impact on survival of the studied factors in patients with poor local and systemic prognosis and extensive bone defects; this may also explain the short-term follow-up in this series. One may argue that patients with metastatic bone disease have more co-morbidities, and radiation therapy as well, putting them at higher risk for complications. In the present study, to reduce the selection bias we included patients with solitary bone metastases with bone destruction and impending

Table 5. Summary of reported cases on cemented and cementless endoprostheses

Authors	*Patients N*	*Site of reconstruction*	*Type of fixation*	*Follow-up (months)*	*Infection (%)*	*Aseptic loosening (%)*
Ahlmann et al. [1]	211	Lower limb*	Cemented	Mean 37.3; range 1-204	5.2	2.4
Bickels et al. [2]	110	Distal femur	Cemented	Median 93.6; range 24-198	5.4	5.4
Zeegen et al. [19]	141	Lower limb*, shoulder	Cemented	Mean 18; range 6-96	7.9	8.7
Gosheger et al. [24]	250	Lower limb*, shoulder	Cementless	Mean 45; range 3-140	12	8
Mittermayer et al. [25]	241	Proximal and distal femur, proximal tibia	Cementless	Median 60; range 11-168	9.7	8.4
Sharma et al. [26]	135	Proximal and distal femur, proximal tibia, proximal and distal humerus	Cemented	Mean 57; median 47; range 1.4-157	8.1	0
Unwin et al. [27]	1001	Proximal and distal femur, proximal tibia	Cemented	Mean 45.7; maximum 287	21.9	7.1
Griffin et al. [31]	99	Distal femur, proximal tibia	Cementless	Median, 24.1; range 0.8-72.6	10	2
Current study	232	Lower limb*	Cemented and cementless	Mean 26.8; median 22.8; range 1-84	Overall: 9.1 Cemented: 10.3 Cementless: 7.7	Overall: 3.2 Cemented: 4.3 Cementless: 1.8

* lower limb: proximal, distal and total femur, and proximal tibia reconstruction

or actual pathological fracture, and favorable tumor histology, good general condition and long disease free interval from the treatment of the primary cancer; in these patients, we believe that wide en bloc resection of the skeletal metastasis is justified.

Second, in our analysis we did not consider the adjuvant treatments the patients had. Chemotherapy was administered in approximately equal number of patients of both groups and the results were close to statistical significance. However, radiation therapy was administered in far more patients who had cemented fixation compared to those with cementless stem fixation. In addition, combination of radiation therapy with chemotherapy sensitizes normal tissues to radiation, and this may cause more complications in relation to radiation therapy alone. We concur that the long survival of the patients after surgery is the most important risk factor for failure of a reconstruction, therefore, in patients with bone metastasis, cemented stem fixation is recommended and radiation therapy is usually administered. Although a significant difference that may have biased our results was not observed, given the different number of patients who had radiation therapy in the two groups our patients' selection may be biased, and the risk for a statistical error is substantial; in this setting, our results with respect to the effect of radiation therapy on stem fixation should be considered with caution. However, although the patient populations were vastly different, the type of stem fixation was the only significant variable in both the univariate and multivariate analysis, while the other studied variables were far from significance in both analyses. Lastly, we believe that since no randomized controlled studies have been published yet with respect to cemented vs cementless stem fixation for lower limb endoprosthetic reconstructions, independent institutional studies, as the present study, are useful in establishing the benefits and the complications of cemented and cementless fixation of lower extremity endoprostheses.

Previous studies have evaluated the survival of various endoprostheses (Table 5). Although the rotating hinge design has been a substantial modification that helped reduce mechanical stresses at the bone-implant interface, the role of cemented or cementless fixation is unclear [5,15,23]. Cemented implants such as hip prostheses have been shown to perform equally well as cementless implants [1,13-15]. Since cementless stems have evolved in the last 25 years, there are longer follow-up results with the cemented implants. Failure rates for cemented and cementless endoprostheses ranging from 17 to 33% at 5 years, and 33 to 52% at 10 years have been reported [1,12,14,16,18,24-26]. In the present series, 12.3% of endoprostheses failed at 5 years because of infection (9.1%) and aseptic loosening (3.2%); failures were significantly lower for the cementless endoprostheses.

Infection remains a serious complication in endoprosthetic reconstruction, with a reported rate ranging from 2 to 40% [1,5,11-15,27]. In the present series, 9.1% of endoprostheses failed and were revised because of infection; survival to infection was statistically significantly higher for the cementless endoprostheses. Nevertheless, we acknowledge that most patients with bone metastasis had radiation therapy and cemented stem fixation; since patients with metastatic disease tend to have more co-morbidities, radiation therapy may have put them at higher risk for infection. Although a statistically significant difference with respect to the sites of reconstructions was not observed, by direct comparison of the numbers the most frequent site of infection was the proximal tibia followed by the distal femur and the proximal femur. The reported rate of aseptic loosening ranges from 2 to 86% at 5 years and 42% at 10 years [1,5,13-15]. In the present series, 3.2% of endoprostheses failed and were revised because of aseptic loosening; no statistically significant difference between the two types of stem fixation was observed. This may be attributed to the reduced rotational stresses transmitted to the stems of the rotating hinge knee prostheses compared to the previous constrained prostheses, the appropriate cement technique and press-fit fixation of stems with optimum diameter, and the surgical experience in oncological operations in specialized centers [12,13,18]. Although no statistically significant difference was observed, the most frequent site of aseptic loosening was the proximal tibia, followed by the proximal femur and the distal femur.

Previous studies reported on the effect of radiation therapy and chemotherapy on the survival of endoprostheses [1,12,24]. The present study showed a trend for significance with the use of chemotherapy, and no significant effect of radiation therapy on survival between cemented and cementless endoprostheses. However, our results regarding the effect of radiation therapy on stem fixation should be considered with caution; most of the patients who had radiation therapy had metastatic bone disease and cemented stem fixation. A previous study [24] showed that the revision rate in patients who weighted >68 kg was 3.6-fold higher compared to patients who weighted <57 kg. Another study [26] showed a higher failure rate from aseptic loosening in young patients compared to adults. The present study did not show any significant relation with these variables. The only significant univariate and multivariate predictor of survival of the endoprostheses was cementless type of stem fixation. However, these observations need to be confirmed in a longer-term follow-up study.

In conclusion, overall survival and survival to infection is higher for cementless vs cemented endoprostheses. Survival to aseptic loosening is not different between the two types of endoprostheses. The type of stem fixation is the only significant variable for survival.

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