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What Is the Long-term Survivorship of Primary and Revision Cemented Distal Femoral Replacements for Limb Salvage of Patients With Sarcoma?

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Abstract

Background Cemented endoprosthetic reconstruction after resection of primary bone sarcomas has been in common use for decades. Although multiple studies have reported the survivorship of primary endoprostheses, implant survivorship after revision surgery is less well established. Given that earlier advances in systemic therapy improved survival of patients with sarcoma, the usage of revision endoprostheses can be expected to increase and, as such, understanding revision implant survivorship will help to inform patient and surgeon expectations. Additionally, as new implants are developed that allow alternative reconstruction options, a normative dataset establishing accurate expectations for revision cemented endoprostheses is a critical benchmark by which to measure progress.

Questions/purposes (1) What is the implant survivorship free of all-cause revision for primary and revision cemented distal femoral replacements (DFRs) used in the treatment of malignant or benign tumors? (2) What are the most common indications for revision of primary and revision DFRs in an oncology population with mean follow-up of more than 10 years? (3) How does the indication for revision of a primary DFR affect the subsequent risk for and type of revision DFR complication? (4) What patient, tumor, or implant characteristics are associated with improved survivorship free of revision in cemented DFRs used in patients treated initially for primary malignant or benign tumors?

Methods This was a retrospective, comparative study using our institution's longitudinally-maintained database of 806 cemented endoprostheses starting in 1980 and assessed through December 31, 2018. In all, 365 DFRs were inserted during this time, but 14% (51 of 365) were placed for nonprimary bone tumors and 1% (5 of 365) were cementless reconstructions, leaving 309 cemented DFRs. Seventy-one percent (218 of 309) were primary implants and 29 percent (91 of 309) were revision implants (used to revise a prior DFR in all patients). During this time period, our strong bias was to use cemented stems and, thus, nearly all of our patients had cemented stems. Six percent (13 of 218) of primary DFRs were implanted more than 2 years before the study end; however, they lacked 2 years of follow-up data and, thus, were considered lost to follow-up, leaving

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Clinical Orthopaedics and Related Research® neither advocates nor endorses the use of any treatment, drug, or device. Readers are encouraged to always seek additional information, including FDA approval status, of any drug or device before clinical use.
Ethical approval for this study was obtained from the University of California-Los Angeles, Los Angeles, CA, USA (number 10-001857-AM-00031).

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205 implants in the primary DFR analysis group. Only the first revision after primary DFR revision surgery was included in the revision cohort analysis. Thirty-two percent (29 of 91) of revision DFRs were second or more revision patients and were excluded, leaving 62 implants in the revision analysis group. Most patients in both groups were men (57% [117 of 205] for primary and 71% [44 of 62] for revision) who had been diagnosed with osteosarcoma (75% [153 of 205] and 73% [45 of 62] for primary and revision, respectively). The primary cohort had mean age of 26 ± 16 years with a mean follow-up of 136 ± 122 months, and the revision cohort had mean age of 31 ± 13 years (p = 0.02) with 141 ± 101 months of follow-up. Study endpoints included all-cause implant revision and cause-specific revision for soft tissue complications, aseptic loosening, structural complications (defined as periprosthetic or implant fracture), infection, or tumor progression. Planned surgery for implant lengthening procedures was excluded. Implant survivorship free from all-cause revision was calculated using a competing risk (cumulative incidence) estimator with death as a competing risk. A log-rank test using chi-square analysis was used to evaluate the differences in implant survivorship between primary DFRs and first revisions. The cause-specific incidences of implant revision were tabulated for primary and revision DFRs. Cox regression analysis investigated the odds of subsequent all-cause revision surgery for revision cemented DFRs based on the primary implant complication. A binary logistic regression analysis using age, gender, indication for revision, tumor type, infection, perioperative chemotherapy, and radiation was performed to identify factors associated with a second DFR reoperation. Relative effect sizes are reported as ORs.

Results The revision DFR cohort had a shorter mean survival to all-cause revision than the primary cohort (mean 10 years [95% CI 7 to 12] versus 18 years [95% CI 15 to 20]; p < 0.001). The most common complications necessitating revision for revision implants were periprosthetic or implant fracture in 37% (23 of 62) and aseptic loosening in 15% (9 of 62), and the type of primary implant complication was not associated with risk of subsequent all-cause revision surgery for revision implants. Stem diameter less than 15 mm was associated with repeat all-cause revision in cemented revision DFRs after controlling for resection length, stem length, implant fabrication (custom or modular), and presence of a porous collar (OR 4 [95% CI 1 to 17]; p = 0.03). No other parameters that we explored, including patient age, gender, chemoradiation history, or primary tumor diagnosis, were associated with repeat revision surgery.

Conclusion Understanding modifiable factors that can improve revision DFR survival is critical to achieving long-term limb salvage for patients with tumors around the knee. Our data suggest that utilizing implants with the largest possible stems—or at a minimum increasing the stem size over the primary implant—is important to revision cemented DFR survivorship and is an important part of our revision practice. Improving revision implants' resistance to aseptic loosening through designs that resist torsion (a common mode of cemented fixation failure)—such as with the use of custom cross-pin fabrication—may be one method to improve survivorship. Another will be improved implant metallurgy that is resistant to fatigue fracture. Next steps may include understanding the optimal ratio of femoral diaphyseal width to implant diameter in patients where anatomic constraints preclude the insertion of cemented stems 15 mm or more in diameter.

Level of Evidence Level IV, therapeutic study.

Introduction

The distal femur is the most common site of primary malignant bone tumors, and multiple reconstruction options exist after resections for tumors about the knee. However, reconstruction with endoprosthetic replacement is the preferred technique because of these implants' modularity, wide availability, and stability, which permits immediate weightbearing [13, 17]. The main causes of reoperation and revision following endoprosthetic reconstruction include aseptic loosening, implant and periprosthetic fracture, and infection [11].

Revision surgery for patients with segmental bone and joint replacement is becoming more common as enhanced survivorship from sarcoma challenges the durability of oncologic reconstructions [25]. Additionally, most patients with sarcoma around the knee are young—notably younger than patients undergoing distal femoral replacement for femur fracture or revision arthroplasty [5]—and thus are expected to outlive their implant while enjoying a more active lifestyle. Endoprosthetic revision is challenging because of limited residual bone stock, poor muscle function, and an abnormal soft tissue envelope [2]. Nonetheless, the success of limb salvage surgery over the long term depends on understanding the factors that can result in reoperations and revisions, as well as how to successfully manage those factors [21].

Numerous studies have reported the survivorship of primary distal femoral endoprostheses and factors associated with implant failure [1, 4, 9, 15-19, 24]. However, far fewer studies exist on the survivorship of revision distal femoral replacements because this requires a very large primary dataset and very long follow-up [2, 21, 25, 26]. It is critical to the long-term success of limb salvage surgery that outcomes of revision endoprosthesis surgery are studied and that data are reported by anatomic location instead of as mixed cohorts so as not to miss location-specific trends [11]. Additionally, as new implants are

developed that allow alternative reconstruction options, a normative dataset establishing accurate expectations for revision cemented endoprostheses is becoming a critical benchmark by which to measure progress.

We therefore asked: (1) What is the implant survivorship free of all-cause revision of primary and revision cemented distal femoral replacements (DFRs) used in the treatment of malignant or benign tumors? (2) What are the most common indications for revision of primary and revision DFRs in an oncology population with mean follow-up of more than10 years? (3) How does the indication for revision of a primary DFR affect the subsequent risk for and type of revision DFR complication? (4) What patient, tumor, or implant characteristics are associated with improved survivorship free of revision in cemented DFRs used in patients treated initially for primary malignant or benign tumors?

Patients and Methods

Study Design and Setting

This study was performed at the University of California-Los Angeles, an urban tertiary referral academic medical center. All study patients were treated by one of the two senior authors (JJE, NMB), both fellowship-trained orthopaedic oncology surgeons whose practice exclusively involves the care of patients with primary malignant and benign bone and soft tissue tumors, including skeletal metastatic disease.

Patients

We retrospectively queried our institution's database of 806 primary and revision endoprostheses placed for oncologic indications (Fig. 1). All primary and revision endoprostheses were implanted by the two senior authors (JJE, NMB) between December 1, 1980 and December 31, 2018. There were 365 DFRs in the database. Fourteen percent (51 of 365) were excluded as they were used in the treatment of metastatic disease and 1% (5 of 365) were cementless reconstructions and were excluded. During this period, our strong bias was to use cemented stems and, thus, nearly all of our patients had cemented stems. Patients were included in the study if they had undergone a primary or revision cemented DFR during treatment for a primary malignant or benign tumor of the femur or thigh (n = 309). There were 218 primary and 91 revision cemented DFRs. Of the 218 primary implants, 6% (13) had surgery performed more than 2 years before study close but lacked at least 2 years of clinical data. Thus, these primary DFRs were considered lost to follow-up (missing), leaving 205 implants in the primary analysis cohort. Only a first revision after primary implant complication was included in the revision implant analysis. Of the 91 revision DFR entries, 32% (29) were excluded for not being a first revision episode. Thus, there were 62 first-revision implants in the analysis cohort, and no revision implant was lost to follow-up or missing. All revision DFRs were used to revise primary endoprostheses (no allografts or other primary reconstructions). Seventy-six percent (47 of 62) of revision DFRs were used to revise primary implants from our primary study cohort, and 24% (15 of 62) were outside referrals indicated for a DFR revision. Of the included patients, 3% (7 of 205) of patients in the primary DFR cohort and 10% (6 of 62) of patients in the revision DFR cohort had not been seen in the last 5 years and were not known to have reached a study endpoint (including death). Of these six patients treated by a revision, 83% (5 of 6) had a stem diameter less than 15 mm, and 17% (1 of 6) had a stem diameter of more than 15 mm.

Baseline Data

Most patients in both groups had been diagnosed with Enneking [8] Stage II osteosarcoma (75% [153 of 205] and 73% [45 of 62] for primary and revisions, respectively). The two groups did not differ in mean follow-up time (136 ± 122 months versus 141 ± 101 months for the primary and revisions, respectively). There were more men in the revision cohort (71% [44 of 62]) versus 57% [117 of 205]; $p = 0.05$), and the revision cohort had a higher mean age (31 ± 13 years) compared with the primary cohort (26 ± 16 years; $p = 0.02$). The revision group also had larger mean implant stem diameters (16 ± 3 mm) compared with the primary cohort (14 ± 3 mm; $p < 0.001$). Patients with primary sarcoma were treated with (neo)adjuvant therapy per the standard protocol for each histology at the time of diagnosis, and all patients in the revision cohort had completed adjuvant oncologic treatment (Table 1).

Surgical Technique

The technique for the primary reconstructions has been described in detail [19]. Tumor resections were performed in accordance with widely accepted oncologic principles, typically using a medial thigh approach for bone tumors [7]. Cemented reconstructions were used exclusively at our institution from 1980 to 2013. From 2013 onward, cemented reconstruction has remained the primary mode of reconstruction unless the patient had (1) anatomy preventing the ability to ream at least to 12.5 mm, (2) short residual bone stock that required a less than 120-mm stem, or (3) preference for biologic fixation with a compressive osseointegration

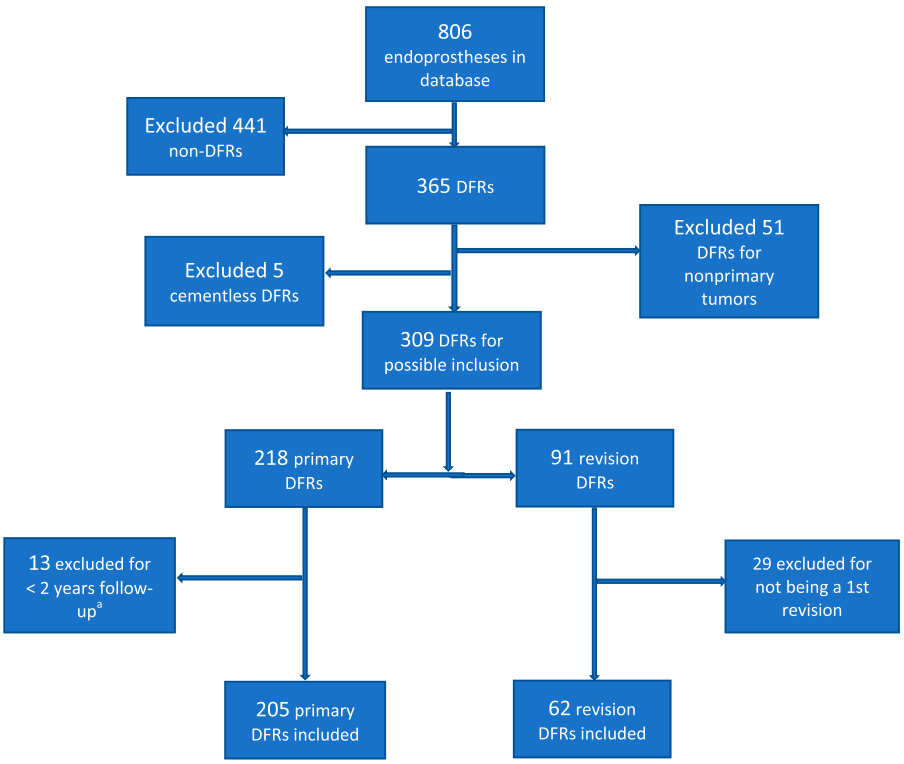

Fig. 1 Flow diagram depicting the development of the primary and revision cemented DFR study analysis cohorts. [a]Six percent (13 of 218) primary DFR patients had surgery performed more than 2 years before study close but lacked at least 2 years of clinical data. Thus, these primary DFRs are considered lost to follow-up or missing.

device. When patient anatomy precludes the use of an 11 x 120-mm cemented stem or larger, cementless implants may be used. All primary reconstructions were performed with antibiotic-impregnated cement (Stryker Simplex P with tobramycin). The tibial components were cemented first, followed by the femoral component with a separate mix. Typical primary cemented stem lengths are 127 mm or 120 mm; in 6% (13 of 205) of patients this was not possible and custom cross-pin cemented stems were used. Primary DFRs included custom and modular designs manufactured by Stryker/Howmedica (79% [162 of 205]), Techmedica (14% [28 of 205]), Dow-Corning Wright Corp (6% [12 of 205]), and Biomet (1% [3 of 205]).

All revision distal femoral replacements were performed through a lateral approach permitting access to the entire femur, if needed, for reconstruction. The implant and cement mantle were removed as atraumatically as possible. Sequential reamers were used to increase the size of the canal by at least 2 mm over the diameter of the explanted stem. A new stem with a diameter at least 1 mm larger than the explant was then cemented into the host femur. In 34% (21 of 62 patients), a custom, cemented stem with cross-pin fixation was used. Intravenous antibiotic administration included preoperative vancomycin, cefazolin, and gentamicin. Cefazolin was continued until deep drains were removed, typically 7 to 10 days postoperatively. Physical therapy was generally unchanged over the course of the study, although whereas continuous passive motion machines and initial bedrest were prescribed historically, modern protocols encouraged patients to bear weight and ambulate as soon as they were able. Patients were then followed at 1-week, 2-week, 6-week, 12-week, and 26-week intervals and then annually after 5 years with serial radiographs and physical examination. Although distal femoral implants have evolved over time, including changes to metallurgy (casted to forged metals around 2003) and design (custom to modular implants in 1990), the surgical techniques, canal preparation, and cementation have remained consistent.

Revision implants included custom-designed and modular implants manufactured by Stryker/Howmedica (79% [49 of 62]), Techmedica (15% [9 of 62]), Biomet (5% [3 of 62), or Dow-Corning (2% [1 of 62]). All implants used a rotating hinge mechanism in the knee.

Table 1. Demographic and clinical characteristics of patients undergoing cemented distal femoral replacement for tumor

Characteristic	Primary cohort (n = 205)	Revision cohort (n = 62)	p value
Gender			
Women	43 (88)	29 (18)	0.05
Age in years	26 ± 16	31 ± 13	0.02
Follow-up in months	136 ± 122	141 ± 101	0.87
Diagnosis			
Osteosarcoma	75 (153)	73 (45)	0.75
Ewing sarcoma	2 (4)	0 (0)	0.27
Chondrosarcoma	6 (13)	6 (4)	0.98
Other	12 (35)	21 (13)	0.48
Tumor stage			
Stage I or benign	12 (25)	11 (7)	0.69
Stage IIA/IIB	71 (146)	55 (34)	0.80
Stage III	13 (26)	10 (6)	0.94
Resection length in mm	150 ± 80	150 ± 83	0.92
Stem length in mm	128 ± 19	131 ± 22	0.72
Stem diameter in mm	14 ± 3	16 ± 3	< 0.001
Fabrication			
Custom	64 (131)	34 (21)	
Modular	36 (73)	66 (41)	0.001
Porous collar			
Yes	62 (128)	73 (45)	0.01
Implant revision			
Yes	38 (78)	65 (40)	< 0.001
Adjuvant therapy			
Chemotherapy	77 (158)	N/A	
Radiation	11 (44)	N/A	

Categorical data are presented as % (n) and continuous variables are presented as mean ± SD.

Variables and Data Sources

Patient data were collected during clinical follow-up encounters and entered into a single longitudinal database. Variables abstracted from this database included age, gender, diagnosis, surgical date, revision date, last follow-up, and chemoradiotherapy exposure (yes or no for this study). Additional procedural and implant variables analyzed included stem length, stem width, segment length, implant modularity (custom versus modular), and femoral resection length, confirmed by pathology reports.

Primary and Secondary Study Outcomes

The primary study outcome was survivorship free from all-cause revision for primary and revision cemented DFR implants. Revision surgery was defined as revision of the stemmed components, removal of the metal body, or amputation. Secondary outcomes included identifying the relative frequency of the most common indications for revision surgery in both primary and revision DFRs, namely: soft tissue complications, aseptic loosening, structural complications (including implant and periprosthetic fracture), infection, and tumor progression. The relationship between the type of first complication and the risk for all-cause revision of the revision implant was investigated, as were factors associated with improved survivorship to all-cause revision surgery in revision DFRs (see Statistical Analysis). The indications for an implant revision were obtained from the database and confirmed with operative reports. The operating surgeon confirmed implant loosening. Aseptic loosening was defined preoperatively based on history (notably weightbearing pain) and radiographs and confirmed intraoperatively by the operating surgeon (JJE, NMB) with inducible gross motion at the bone-cement or implant-cement interface in the setting of negative preoperative laboratory findings for infection and negative intraoperative deep cultures. Bushing changes or planned expansions of growing constructs were

not considered implant revisions. Time to revision surgery for each revision indication was defined from the date of the index surgery to the date of revision or amputation. Two orthopaedic surgeons (EJG, DG) independently analyzed the database and available radiographs to limit misclassification bias of revision indications. Any instances of disagreement were referred to the senior author (NMB) for adjudication.

Ethical Approval

We obtained institutional review board approval for this study.

Statistical Analysis

We used a competing risks (cumulative incidence) estimator to generate survivorship curves with all-cause implant revision as the endpoint. Given the risk of death from oncologic disease or related causes, death was treated as a competing risk [22]. The log-rank (Mantel-Cox) test was used to identify differences in implant survivorship between primary DFRs and first revisions. Differences in patient demographics, diagnoses, staging, treatment variables, and implant characteristics between the primary and revision cohorts were evaluated using a chi-square test for categorical variables and independent sample t-test for continuous variables. We used a Cox regression analysis to assess the relationship between the primary implant's revision indication with the risk of the second DFR revision for any reason. We performed a Cox regression analysis to identify factors associated with revision DFR reoperation carrying forward all variables from the univariate analysis (Supplementary Table 1; http://links.lww.com/CORR/A899). This was performed with three different groupings of predictor variables to avoid over-fitting the model. The variables were grouped as patient factors (gender, age, perioperative chemotherapy, and radiation exposure), implant factors (porous implant surface, implant fabrication [custom versus modular], resection length, stem length, stem diameter, and presence of custom cross-pins), and tumor factors (type and stage). Age at the time of surgery was divided into a binary variable, with age 18 years as the cutoff distinguishing pediatric and adult patients. Other continuous variables including resection length, stem length, and stem diameter were given a cutoff based on the median values of the primary DFR cohort. Relative effect sizes are reported as ORs. All statistical analyses were performed with SPSS Version 25.0 (IBM Corp). All p values were two-sided and $p < 0.05$ was considered significant.

Results

Survivorship of Primary and Revision Cemented DFRs

Primary cemented DFRs exhibited superior survivorship to all-cause revision with death as a competing risk compared with revision DFR implants (Fig. 2). The mean time to implant revision for primary DFRs in this cohort was 18 years (95% CI 15 to 20), and the mean time to revision for revision implants was 10 years (95% CI 7 to 12; $p < 0.001$). At 15 years, the survivorship free from all-cause revision with death as a competing risk was higher in the primary DFR group (52% [95% CI 43% to 61%]) compared with the revision group (23% [95% CI 9% to 37%]; $p = 0.01$). At 20 years, survivorship was also superior for the primary compared with revision DFR group (46% [95% CI 35% to 55%] versus 9% [95% CI 0% to 19%]; $p = 0.009$) (Supplementary Table 2; http://links.lww.com/CORR/A900).

Most Common Indications for Revision of Primary and Revision DFRs

The most common indications for revision of cemented DFRs in our primary and revision cohorts were for structural complications (including implant or periprosthetic fracture) or aseptic loosening (Fig. 3). The most common indication for primary implant revision was for structural complications, occurring in 14% (29 of 205) of implants, followed by aseptic loosening (13% [27 of 205]). Of these primary structural complications, 48% (14 of 29) were implant fatigue fractures, 3% (1 of 29) were periprosthetic fractures, and 48% (14 of 29) were not further specified. Six percent (13 of 205) of primary

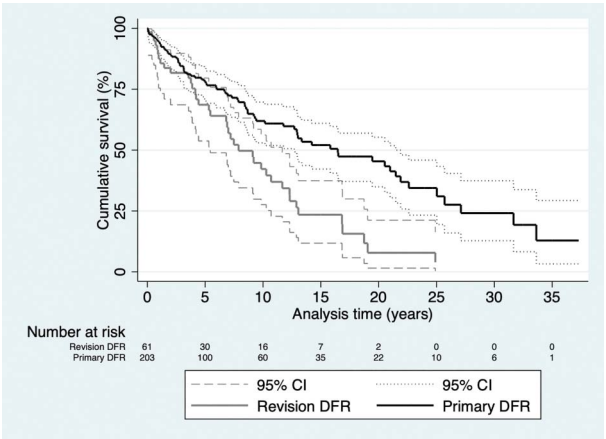

Fig. 2 A competing risks estimator curve comparing overall implant survival (with death as a competing risk) between primary and revision cemented distal femoral replacements (log-rank, $p < 0.001$).

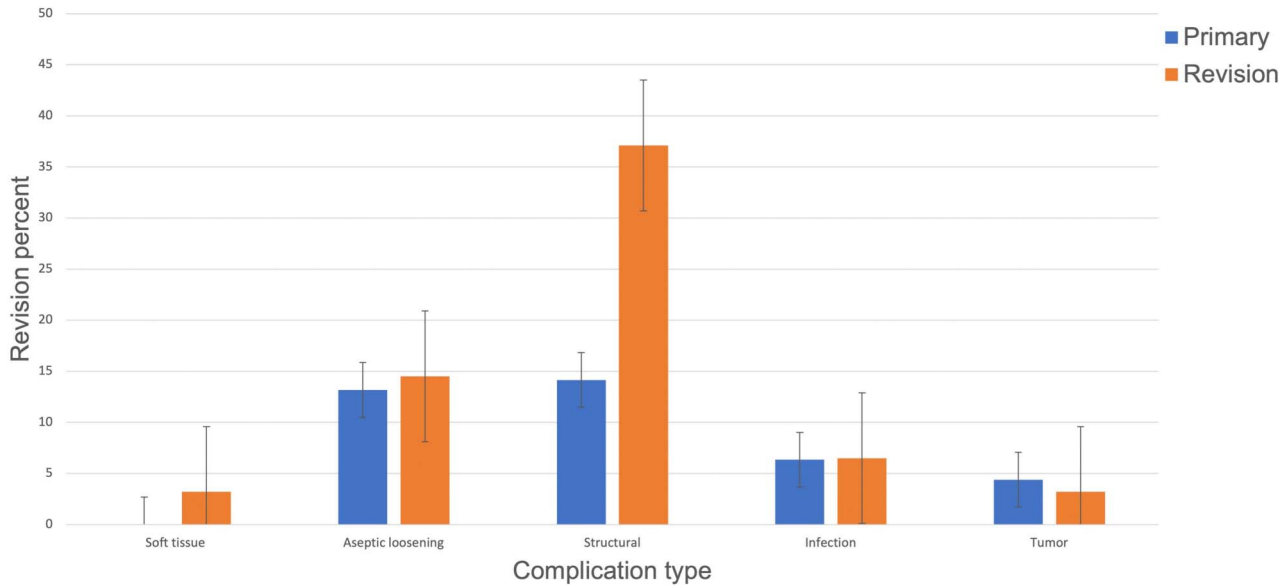

Fig. 3 This figure shows the distribution of revision surgery indications for primary and revision cemented distal femoral replacements. A color image accompanies the online version of this article.

implants were revised for infection, and 4% (9 of 205) underwent reoperation (amputation) because of tumor progression. Similarly, for revision implants in our cohort, the dominant indication for revision was structural complications (37% [23 of 62]). Of these structural complications, 30% (7 of 23) were implant fatigue fractures, 13% (3 of 23) were periprosthetic fractures, and 57% (13 of 23) were not further specified. Fifteen percent (9 of 62) of revision implants underwent revision for aseptic loosening, and 6% (4 of 62) of revision DFRs were revised because of infection. All of these revision implants (four patients) complicated by infection resulted in amputation.

Association Between Primary and Subsequent Revision DFR Complications

The primary implant revision indication was not associated with cause-specific revision DFR complications. Further, the indication for primary cemented DFR revision surgery was not associated with subsequent risk of all-cause revision for revision implants in our cohort. The most common indication for subsequent revision of a cemented revision DFR implant was for structural complications (implant or periprosthetic fracture) irrespective of the primary DFR revision indication (Table 2). Implants used to revise primary DFRs after aseptic loosening did not have an elevated risk of subsequent all-cause revision (OR 4.1 [95% CI 0.9 to 17.5]; p = 0.06) (Table 3).

Patient, Tumor, or Implant Characteristics Associated With Improved Revision Survivorship

Revision implants with narrower stems exhibited decreased survivorship to all-cause revision (Fig. 4). Specifically, cemented revision DFRs with stem diameters smaller than 15 mm had a higher odds of all-cause revision

Table 2. Association between primary cemented DFR and subsequent revision cemented DFR complications

	Type of revision implant complication					
Primary DFR complication	**Soft tissue**	**Aseptic loosening**	**Structural[a]**	**Infection**	**Tumor progression**	**Total**
Soft tissue	0	0	0	0	0	0
Aseptic loosening	1	3	13	4	2	23
Structural	1	4	10	0	0	15
Infection	0	2	0	0	0	2
Tumor progression	0	0	0	0	0	0
Total	2	9	23	4	2	40

[a]Includes implant and periprosthetic fracture.

Table 3. Odds of subsequent all-cause revision surgery for revision cemented DFRs based on the primary implant complication

	Risk of second all-cause revision	
First revision indication[a]	OR (95% CI)	p value
Aseptic loosening	4.1 (0.9-17.5)	0.06
Structural[b]	2.8 (0.62-12.4)	0.18
Infection	0.36 (0.08-1.6)	0.18

[a]No primary DFRs were revised for soft tissue complications, and no revision DFRs were implanted after tumor progression complicated a primary DFR.
[b]Including implant or periprosthetic fractures.

compared with implants with stem diameters of 15 mm or more (OR 4.3 [95% CI 1.1 to 16.6]; p = 0.03) after controlling for implant and resection factors such as resection length, stem length, implant fabrication, and presence of adjuvant cross-pin fixation (Table 4). The mean time to all-cause revision for revision implants with less than 15-mm-diameter stems was 3.2 years (95% CI 2.3 to 4.1) compared with 9.9 years (95% CI 7.7 to 12.2; p = 0.02) for revision implants with at least 15-mm stems. Whereas no revision cemented DFRs with stem diameter less than 15 mm survived 5 years, the 5-year survivorship of revision implants with stems 15 mm or more was 74% (95% CI 58% to 85%; p value not calculable) (Supplementary Table 3; http://links.lww.com/CORR/A901). Sixty-seven percent (4 of 6) of the reoperations after the use of stems less than 15 mm in diameter were for structural complications (all stem fatigue fractures) and 33% (2 of 6) were for aseptic loosening. Custom cross-pin fixation was not associated with improved survivorship for aseptic loosening in cemented revision DFRs (Fig. 5). Although no cemented revision DFRs with cross-pins underwent reoperation for aseptic loosening at 10-year follow-up, the 10-year survivorship to aseptic loosening for stems without cross pins was 64% (95% CI 37% to 81%; p = 0.14). No other parameters that we explored, including age, gender, diagnosis, and chemoradiation exposure, were associated with revision DFR survivorship.

Discussion

The distal femur is the most common site for primary malignant bone tumors, and endoprosthetic reconstruction has become the preferred method of reconstruction after limb salvage surgery because of the immediate stability and modularity of these implants [13, 17, 18]. Because of enhanced sarcoma survivorship, the increased demands placed on implants by young patients, and the well-documented revision risks of endoprostheses [11], the incidence of endoprosthesis revision surgery will continue to increase. Few studies exist on the survivorship of revision DFRs because this requires a very large primary dataset with long-term follow-up [2, 21, 25, 26]. Using our institutional dataset to study 267 primary and revision cemented DFRs, we found that revision implants have a shorter mean time to all-cause revision than primary implants (10 versus 18 years) and that the most common indication for revision of both implant types was for mechanical complications (including implant and periprosthetic fracture). We also found that a revision stem diameter less than 15 mm was associated with all-cause revision DFR reoperation, and we suggest cross-pin fixation as construct customization to improve resistance against aseptic loosening. Based on our findings, surgeons may aim to not only increase implant stem diameter when revising primary cemented DFRs but also to specifically insert revision stems 15 mm or more when anatomically possible or consider accessory designs that will resist torsion (a common mode of cement fixation failure).

Limitations

Our study has several limitations. First, it is a retrospective study, thus limiting the amount of data we can obtain from the medical record, and it lacks a uncemented comparison group. The endoprosthesis registry at our institution is longitudinally maintained, which may help limit recall and misclassification bias. However, a clear shortcoming is not having complete detail on the proportion of implant versus periprosthetic fractures for the structural complications in our cohort. Although often categorized together, the etiology and possible prevention of each are quite different. Differentiating these outcomes consistently in future

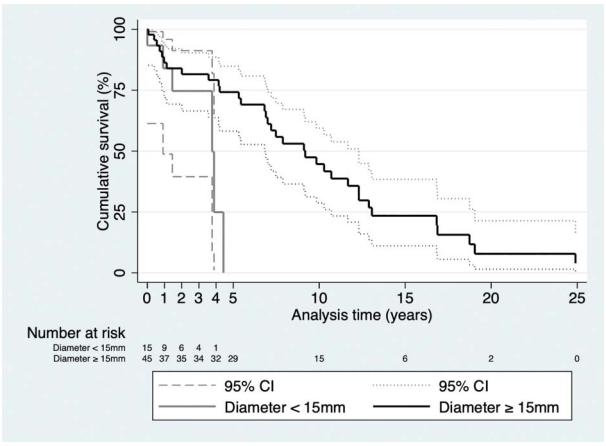

Fig. 4 Competing risks estimator curves representing revision cemented distal femoral replacement survivorship to all-cause revision, stratified by stem diameter < or ≥ 15 mm (log-rank, p = 0.02).

Table 4. Multivariable Cox regression analyses for factors associated with a second revision of cemented revision DFRs

Implant factor	OR (95% CI)	p value
Collar		
Porous (vs nonporous)	2.3 (0.7-7.4)	0.18
Fabrication		
Modular (vs custom)	0.57 (0.23-1.4)	0.22
Resection length		
< 150 mm	0.54 (0.23-1.29)	0.17
Stem length		
< 127 mm	0.65 (0.17-2.5)	0.53
Stem diameter		
< 15 vs ≥ 15 mm	4.3 (1.1-16.6)	0.03
Cross pinning		
Yes	1.2 (0.52-2.8)	0.68
Patient and tumor factor	**OR (95% CI)**	**p value**
Gender		
Men (vs Women)	0.57 (0.26-1.2)	0.16
Age in years		
< 18	1.5 (0.61-3.8)	0.37
Chemotherapy (yes vs no)	0.99 (0.38-2.6)	0.98
Radiation (yes vs no)	0.9 (0.34-2.4)	0.83
Diagnosis[a]		
Osteosarcoma	2.5 (0.74-8.5)	0.14
Ewing sarcoma		
Chondrosarcoma	2.9 (0.7-12)	0.14
Other	0.53 (0.18-1.5)	0.25

[a]Benign tumors are the reference group.

studies is warranted. Second, there could be selection bias when multiple reconstruction options exist for a patient. Our preference has been cemented stem fixation for distal femur reconstructions. When this is precluded by anatomic constraints (such as small intramedullary canal diameters of very young patients or short residual femora after large resections), then press-fit or compressive osseointegration implants may be used. These reconstructions may be at a higher risk of revision because of the magnitude of the resection [17]. Nonetheless, the consistency with which cemented stems are used in our institution helps to limit this bias, and our results remain generalizable and valuable to cemented stem reconstructions in practice. Third, this was a single-institution study, with all operations performed by two surgeons (JJE, NMB). However, what is lost in terms of generalizability may be offset by the consistency of approaches used. Similar to many endoprosthesis studies, we had a limited patient population. Our study may be underpowered to detect other factors independently associated with revision implant reoperation and may be underpowered to detect a statistical difference in the survivorship free from aseptic loosening with the use of cross-pins. Thus, we have refrained from drawing conclusions when no difference was seen in the data. But given the rarity of sarcoma, this is one of the largest studies focused on primary and, certainly, revision implants with a single anatomic focus and uniform method of stem fixation. Transfer bias also exists when patients are lost to follow-up, as it is possible that they had experienced complications and then sought care elsewhere. Since only 6% of our primary DFR cohort was considered lost to follow-up, the impact of transfer bias is likely minimal. If all patients lacking follow-up had undergone prosthetic revision, the difference in primary and revision DFR survivorship may be less substantial than our data show. We also lacked outcomes scores for patients as all outcomes were based on the need for reoperation. Fortunately, we did not have any patients in need of revision surgery who were unable to be treated due to infirmity, thus limiting this assessment bias. However, patient-reported outcomes after primary and revision DFR in an oncology population would strengthen this study and are needed in future studies more broadly. Lastly, the long study period includes several implant manufacturers and an evolution of implant designs over time, some of which are no longer in production. This heterogeneity is weighed against the long follow-up available, which gives us the ability to identify late implant complications and helps surgeons frame clinical conversations with patients surviving with DFRs today. A similar study of modern implants is clearly needed but remains many years away. Finally, we did not perform an analysis by gender. Certainly, the findings drawn from a mixed population may not apply to each gender equally and separately. However, we did not find gender to impact DFR survivorship in our models (it has not been associated

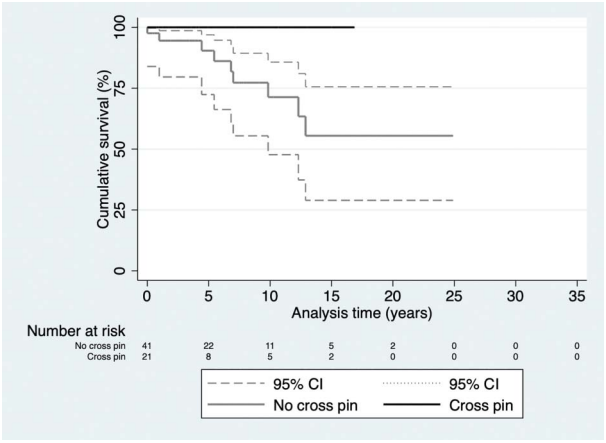

Fig. 5 Competing risks estimator curves representing revision cemented distal femoral replacements, stratified by the use of custom cross-pin fixation (log-rank, p = 0.06).

with primary implant revision risk [17]), and further dividing our study population according to gender would limit our statistical power. Studying patient-reported outcomes after sarcoma reconstructions by gender, as well as the impact of gender on late implant survivorship, are both warranted.

Survivorship of Primary and Revision Cemented DFRs

Primary cemented DFRs exhibited superior survivorship to all-cause revision with death as a competing risk compared with revision DFR implants, and the survival gap widened as length of follow-up increased. The survivorship of cemented primary DFRs in this study is comparable to that reported in others, although the follow-up of primary implants (mean 136 months) is one of the longest currently reported. Survivorship of primary cemented DFRs at 10 years and 20 years has ranged from 50% to 70% and from 30% to 50%, respectively [13, 14, 16, 20, 24]. We extend these findings to primary implant survival of 23% at 30 years, although our results should be interpreted in the context of the fact that very few patients remained in the study at this late point.

The relative survival time of revision cemented DFRs in patients with tumors has been harder to study robustly because of their rarity. Prior studies have found that DFRs used in revision reconstruction have worse survivorship than cemented DFRs placed for primary reconstructions [5, 6]. Only two previous studies have reported data on revision cemented DFRs in oncology, both in the context of mixed anatomic cohorts. Shin et al. [21] reported that 34% (12 of 35) of revision endoprostheses went on to subsequent revision surgery after a mean follow-up of 68 months. Ten-year survival for the 19 revision endoprostheses around the knee was 38% (similar to our mean of 42%). The only other study is an early report from our institution more than 20 years ago [25]. Wirganowicz et al. [25] studied 48 revision cemented endoprostheses (mostly DFRs) and reported a revision implant reoperation rate of 34% at 7 years after surgery (compared with our rate of 58% at 10 years). Interestingly, their Kaplan-Meier analysis found no difference in the average time to revision surgery between the primary to first revision and between the first revision to second revision procedures, which contrasts with our results generated from more implants evaluated over a longer time using a competing risks estimator. Although a smaller study with short-term follow-up also demonstrated equivalent outcomes [12], other studies of cementless revision DFR in patients having had sarcoma support an increased rate of reoperation in revision implants [18, 26]. This emphasizes the importance of follow-up, and the strength of our study is that we could study a large cohort over a long period of time. Our data should help surgeons in the management of patient expectations perioperatively and while monitoring implant survival postoperatively. We believe it is important to surgeons (and patients) that each understand that outcomes after revision surgery (particularly implant survival) will not be the same as after their primary surgery. This helps surgeons inform patient expectations, and accurately managing patient expectations perioperatively is important for maintaining trust in the clinical relationship.

Most Common Indications for Revision of Primary and Revision DFRs

In our study, the most common indications for revision surgery with cemented primary and revision DFR were implant or periprosthetic fracture and aseptic loosening. In a multi-institutional cohort including 951 primary DFRs, infection was the most common revision indication (30% [79 of 261]), whereas their review of 2861 primary DFR implants from studies of others found aseptic loosening and structural complications to be the most common indications for primary implant revision (43% and 21% of 761 revisions, respectively), which supports our findings [11]. A critical message of this study was the need to report endoprosthesis outcomes by anatomic location because heterogenous groups miss anatomy-specific trends. In the reports from Shin et al. [21] and Wirganowicz et al. [25], the most common indication for repeat cemented DFR revision was aseptic loosening. We have extended these studies with a larger, homogenous cohort and longer-term follow-up. Our results interpreted in the context of existing evidence suggest that modern design strategies should focus on increasing DFR resistance to aseptic loosening and structural implant complications.

Association Between Primary and Subsequent Revision DFR Complications

We did not find an association between the indication for primary DFR revision and the risk of all-cause repeat revision of the revision implant. Revision for aseptic loosening was not associated with an increased risk of subsequent all-cause revision, although this may have been caused by a Type II statistical error (insufficient sample size). We found that a revision DFR was itself most commonly revised for structural complications (implant or periprosthetic fracture) irrespective of the primary implant's revision indication. Although studies on the relationship between primary and revision endoprosthesis reoperations are limited, Theil et al. [23] studied 599 primary and 234 revision implants, which included 114 mostly uncemented DFRs. In their analysis, which

combined anatomic locations, the indication for primary implant revision was not associated with subsequent all-cause revision risk. However, the authors found that the type of first complication was associated with the type of revision complication. Like the present study, implants used to revise primary structural complications were most commonly revised themselves for structural reasons. This included 38 instances of repeat structural complications in 114 revision DFRs (67% of all revision DFR reoperations).

Patient, Tumor, or Implant Characteristics Associated With Improved Revision Survivorship

Our data revealed a stem diameter smaller than 15 mm in cemented revision DFRs was uniquely associated with all-cause implant revision after controlling for implant and patient characteristics such as gender, diagnosis, resection and stem length, and chemoradiation exposure. Our data suggest, therefore, that inserting as large a diameter cemented stem as possible is advantageous, and this has now become an important part of our revision practice [2]. Factors associated with primary DFR revision are well studied [1, 9, 10, 15, 17, 19]. Factors independently associated with revision surgery for revision cemented DFRs have not been reported to our knowledge. In a study of a mixed-anatomy, mostly cementless cohort, Theil et al. [23] identified total bone reconstructions, diabetes, and preoperative radiotherapy as factors associated with an increased risk of second prosthetic complications. However, these factors are patient- or tumor-specific and largely out of the surgeon's control. Modifiable factors, such as implant characteristics, have not been identified. The importance of stem diameter to the survival of cemented and press-fit primary DFRs has been reported [1, 9]. Bergin et al. [1] reported that the mean stem diameter of stable implants in their cemented primary DFR series was 14.5 mm (similar to our findings), and the average stem diameter of implants that were revised for aseptic loosening was 10.7 mm. Although these prior reports calculated that a diaphyseal bone to stem diameter ratio of 2.5 or more was associated with risk of aseptic loosening, we were not able to calculate this ratio for our revision cohort. Validating this calculation in revision implant populations is warranted. Given that studies have identified aseptic loosening as a common indication for revision cemented DFR reoperation [21, 25], any strategy for mitigating this long-term risk in revision implants is important. This report enhances the evidence for studying factors associated with cemented revision DFR reoperation with multivariate models. Our data suggest custom cross-pin fixation is associated with increased resistance against loosening of revision cemented DFRs, as our group previously has reported in mixed-anatomy cohorts [3].

Conclusion

In our present series, we found that revision cemented DFRs are more likely to undergo revision (and earlier revision) than primary implants. Additionally, the most common indications for repeated revision of cemented DFRs were for implant fracture and aseptic loosening. Understanding modifiable factors that can improve revision DFR survival is critical to achieving long-term limb salvage for patients with tumors around the knee. Utilizing implants with the largest possible stems—or at a minimum, increasing the stem size over the primary implant—is an important part of our revision practice. Improving revision implants' resistance to aseptic loosening through designs that resist torsion (a common mode of cemented fixation failure)—such as with the use of custom cross-pin fabrication—may be one method to improve survivorship. Another will be improved implant metallurgy that is resistant to fatigue fracture. Next steps may include understanding the optimal ratio of femoral diaphyseal width to revision stem diameter in patients where anatomic constraints preclude the insertion of cemented stems larger than 15 mm. Finally, we suggest improving data collection and reporting around endoprosthesis revision by not combining dissimilar outcomes into a common category of structural complications. Implant fracture has its own unique causes and possible solutions, while periprosthetic fracture may be more related to patient activity, bone mineral density, or overall health. Understanding the relative frequency of these complications separately will help clinicians better monitor risk factors for each prospectively and intervene (for example, offering medication to support bone mineral density), if indicated. Currently, we continue to primarily utilize cemented stem endoprosthetic reconstructions for tumors around the knee and believe these data support that preference. The durability and reliability of this technique has been demonstrated definitively in the primary setting, and although survivorship of revision cemented surgery is shorter than that for primary implants, it can be accomplished routinely while minimizing trauma to the remaining bone. It is our opinion that cemented stem reconstruction is optimal and is supported by data that equal or supersede those available for cementless reconstructions.

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