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Long-term Outcomes of Cement in Cement Technique for Revision Endoprosthesis Surgery

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Abstract

Introduction

With considerable advances in imaging, implant design, surgical technique and chemotherapeutics, limb salvage surgery has supplanted amputation as the preferred intervention for the majority of patients with a musculoskeletal malignancy.[1–3] As the ability to treat these malignancies becomes progressively more sophisticated, the utilization of endoprostheses continues to expand, and the survival of patients undergoing endoprosthetic reconstruction continues to improve. With 25-year implant survival rates reported to be approximately 50%, an increasing number of patients will require revision of their endoprosthesis.[4–6]

The treatment of patients with endoprosthetic failure presents a challenge due to resultant insufficient bone stock, poor muscle function and lack of normal soft tissue coverage. A prior study by Kabo et al. documented a 7-year survival of 66% for revision endoprostheses, reflecting the difficulty of creating a durable construct in a revision setting.[5] In particular, the revision of cemented endoprostheses is technically demanding. The removal of the implant from stress shielded bone is often fraught with challenges and the ease of simply “cutting above” the cement mantle is tempting for surgeons. This, however, uses additional bone stock and dramatically limits the number of revisions a patient can undergo in their lifetime. It also raises the level of amputation if a complication arises for which limb salvage is no longer an option. More conservative revision techniques have been described including converting to a short compression fixation device (ZimmerBiomet Compress), custom cross-pin fixation, telescoping method, and using a cement-in-cement revision technique.[7–13] While Compress and custom cross pin fixation have shown encouraging results as a revision technique, data is all from small series and the implants often require FDA and IRB approval, delaying the surgery many weeks. The CiC revision technique is thus an appealing option as it does not utilize additional bone stock and uses off-the-shelf implants.

Given the limited options available for cemented endoprosthetic revision and the potential of the CiC revision technique as a conservative and repeatable procedure, we sought to answer several questions. Primarily, we endeavored to understand the long-term survival of and complications from the cement in cement (CiC) revision technique and subsequent revisions. Additionally, we investigated the influence of failure mode and anatomic location on prosthesis survival.

Methods

This is a retrospective review of our endoprosthesis database consisting of 512 consecutive cemented endoprosthetic reconstructions performed for oncologic diagnoses between 1980 and 2014. Research approval was granted by the Institutional Review Board. All primary endoprostheses were implanted by the senior author (JJE) at a single institution. Revisions were performed by the senior and lead authors (JJE and NMB). Follow-up was performed at a single institution and data was prospectively entered into a single database.

Patients were identified for inclusion in the study if they were revised at the cement-implant interface using a CiC revision technique. Patients were excluded if the revision surgery included bushing changes, revisions for adjacent joint pathology, revisions into native bone or adjacent joints (total femur endoprostheses), and planned expansions of growing implants. Patients with upper extremity implants were excluded as the rotational stress placed on the cement is dramatically less than that for lower extremity patients. Patients with endoprostheses originally placed for non-oncologic diagnoses were excluded as they often had undergone multiple operations by outside physicians before endoprosthetic reconstruction. Patients all had chemotherapy and/or radiation as per protocol for their underlying diagnosis at the time of their original endoprosthesis placement. No patient was actively receiving chemotherapy or radiation at the time of the CiC revision.

Of the 512 patients who underwent cemented endoprosthetic reconstruction of the lower extremity for oncologic disease, 54 (10.5%) underwent a CiC revision (mean age 32 years, range 13 – 81). Mean follow up from CiC revision was 127 months (range 6 – 326 months).

Surgical Technique

All primary endoprosthetic reconstructions were performed by the senior author (JJE) and revisions were performed by either the lead or senior author (NMB or JJE). Our surgical technique for primary implantation has been reported in full previously.[6, 14] Primary tumor resections were in accordance with widely accepted oncologic principles.[14–17] All primary reconstructions were implanted with antibiotic-impregnated cement (Stryker Simplex P with Tobramycin, Mahwah NJ) using modern generation cement technique.

The cement-in-cement revision technique was used for all patients during the study for whom i) the cemented stem of the endoprostheses was noted to be loose or fractured, ii) the remaining bone stock retained a cylinder of bone of at least 127mm in length to accept a standard 5inch stem. Patients with insufficient bone stock for this revision technique (defined by the operating surgeon as an absence of an intact cylinder of bone of sufficient length to accept a standard stem) were revised with alternative techniques (cross pin fixation, total femoral replacement, amputation, or, in the last five years, conversion to compressive osseointegration implants) (Figure 1).

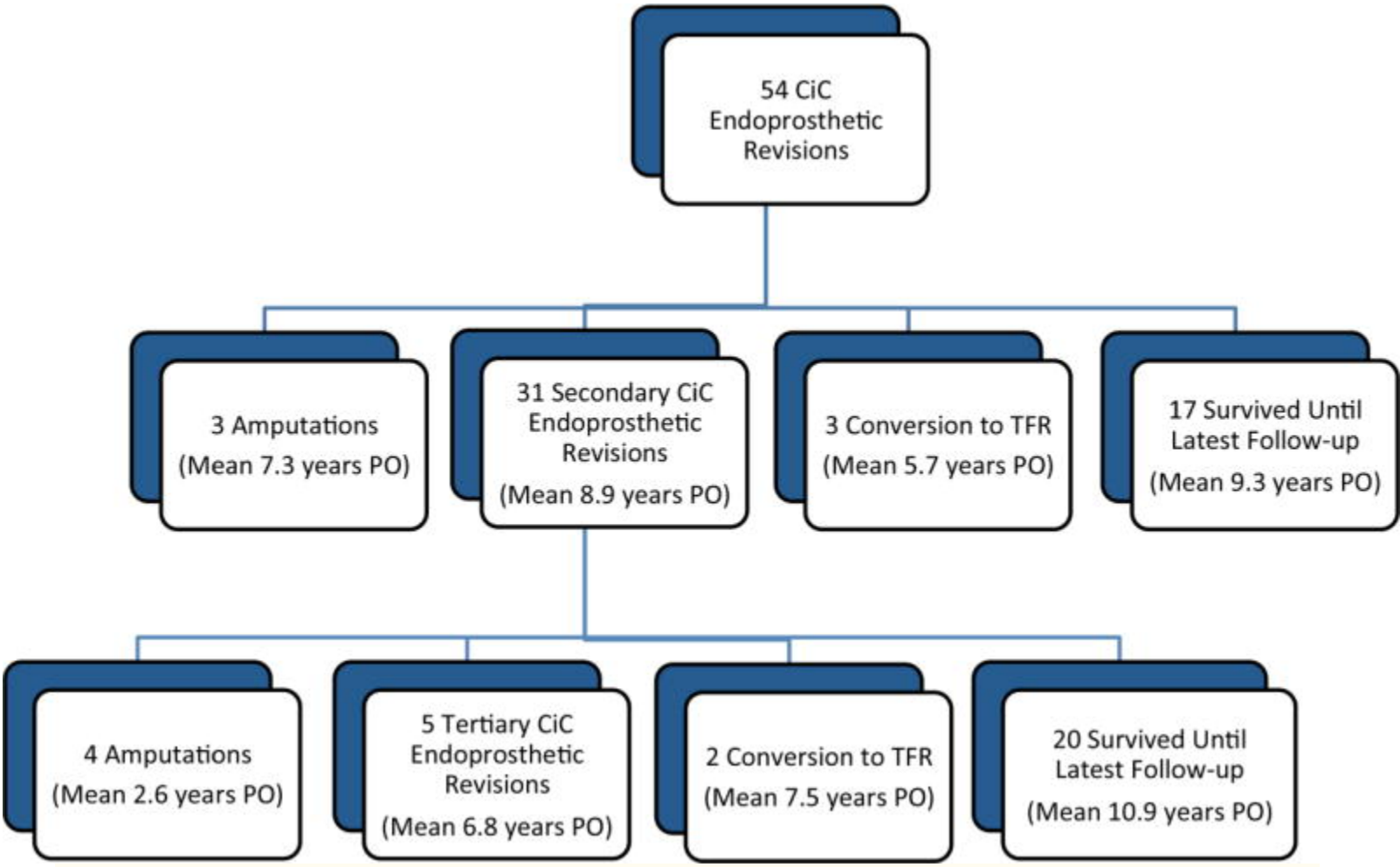


Figure 1

Distributions of outcomes for 54 endoprosthetic revisions with 8.9 years of post-operative follow up including amputation, CiC revision, conversion to TFR, and continued survival. In the second tier, distributions of endoprosthetic revisions with 4.5 years of post-operative follow up including amputation, tertiary CiC revision, conversion to TFR, and continued survival.

The indication for cement in cement revision surgery was taken from the endoprosthesis database and confirmed with a review of the operative report. Loosening was determined by the operating surgeon in preoperative consultation and intraoperatively. In general, patients who developed weight bearing pain that was activity dependent were evaluated with radiographs and a physical exam. If radiographic evidence of loosening was noted (between the implant and the cement or the cement and the bone) by the operating physician, or pain did not improve within 4 weeks of crutch immobilization, the patient had a laboratory workup for infection. If no infection was noted, the patient was taken to the operating room for revision of the endoprosthesis. At the time of revision, all cemented stems were manually tested for loosening or structural failure. Structural failure is defined as “periprosthetic or prosthetic fracture or deficient osseous supporting structures”.[9]

Revision with the CiC technique followed several principles: All revisions of the femur were done through a lateral approach irrespective of the location of the initial resection so that complete exposure could be achieved. The previous implant was removed as atraumatically as possible, with emphasis on maintaining an intact cylinder of bone for re-cementation. In the case of bone-cement-interface failure, the cement mantle would be extricated with minimal effort. In the case of cement-implant-interface failure, a cement mantle would remain in the intramedullary canal after implant extrication. Reverse curettes and an Oscar 3® Comprehensive Revision Instrument (Orthosonics, Chatham, NJ) were used to clear residual cement, with the goal of widening the existing canal to at least 2mm wider than the diameter of the explanted implant. Sequential reamers were also used to clear a concentric path for the revision implant. Care was taken not to perforate the canal so that

repressurization into the cement mantle could be achieved with new cement. The canal was cleaned with a brush. A stem at least 1mm larger than the explanted stem was then cemented into the pre-existing cement mantle, using a modern generation cement technique. In the event of a canal perforation, which occurred generally anteriorly during cement or implant extraction in the femur, the wound was opened such that direct visualization of the defect was achieved. The cement was then placed with the surgeon's thumb placed directly over the defect to ensure full pressurization of the cement. Once the cement hardened, allograft struts and Dall-Miles® cerclage cables (Stryker, Mahwah, NJ) were placed to reinforce the bony defect. Care was taken to confirm bone length and appropriate rotation.

Intravenous antibiotics dosing protocol evolved over time but for the last 15 years, preoperative antibiotics consisted of vancomycin, gentamicin, and cefazolin. In all cases, antibiotics were continued until the drain was removed, typically after 7 – 10 days. Patients were made weight bearing as tolerated immediately after the procedure. Patients were followed clinically at 1, 2, 4, 8, 12, and 26-week follow-up visits with serial radiographs, followed by 6-month follow-ups thereafter. Range of motion was encouraged at all follow-up visits. Patients were encouraged to limit high-impact activities. Symptoms of pain, instability, or fever indicated potential problems.

All primary endoprostheses initially were custom designed by one of three manufacturers: Stryker/Howmedica (Mahwah, NJ) (n = 41), Techmedica (Camarillo, CA) (n = 11), and Dow-Corning Wright Corp (Arlington, TN) (n =2). For prostheses involving the knee, a rotating hinge mechanism (Kinematic®, Howmedica, Noiles®, Techmedica or Lacey®, Wright Medical) was utilized. Revision prostheses included both custom designed and modular systems.

Patient data was collected from each clinical follow-up point into a single database. Variables assessed included: name, age, sex, diagnosis, date of surgery, date of revision, date of last follow-up, procedure performed, implant type, chemotherapy or radiation, and complications. Complications including mechanical failure, infection or local recurrence were recorded.

At each follow-up visit, patients were assessed by the revised Musculoskeletal Tumor Society functional evaluation (MSTS).[18, 19] For this system with a range of 0 – 30 points, the functional assessment is based on the analysis of subjective factors (pain, functional activities, and emotional acceptance), and factors specific to the upper extremity (positioning of the hand, manual dexterity and lifting ability) or the lower extremity (use of external supports, walking ability and gait). The MSTS score was determined by the senior and lead author independently at the most recent follow-up visit. Range of motion was assessed clinically. Standard orthogonal radiographs were assessed at each postoperative visit. Failure type was categorized according to the method by Henderson et al.:[9] soft tissue failure (1), aseptic loosening (2), structural failure (3), infection (4), or tumor progression (5). Specifically, structural failure is defined as, "periprosthetic or prosthetic fracture or deficient osseous supporting structure."[9] Bias was addressed by having three surgeons independently analyze the database and classifications.

A Kolmogorov-Smirnov normality test was used to determine if the data were normally distributed. Kaplan-Meier analysis was used to assess survivorship of the prosthesis. This analysis censors patients that were lost to follow up and accounts for their data in its survival estimation.[20] Survival analysis was performed with the statistical software SAS-JMP (JMP®, Version *12*. SAS Institute Inc., Cary, NC, 1989–2007). Revision cases were categorized by initial revision versus subsequent revision and by location of revision. Two-tailed student t-tests and Mann-Whitney rank-sum tests were used to analyze differences within normally and non-normally distributed variables, respectively. Spearman rho was used for nonparametric correlation. A p value of < 0.05 was considered to be significant.

Results

Demographics

The 54 patients who underwent CiC revision and were included in the study had a mean age of 32 at time of index CiC surgery (range 13 – 81). 63% (34/54) of patients were male and 37% (20/54) were female. No patient received perioperative chemotherapy or radiation therapy at the time of the revision surgery. 41/54 (76%) patients underwent CiC revision of a DFR, 6/54 (11%) patients underwent CiC revision of a PFR, 6/54 (11%) patients underwent CiC revision of a PTR, and 1/54 (2%) patient underwent CiC revision of an

intercalary reconstruction. Thirty-one patients underwent subsequent CiC revision, with 23 DFR, 5 PTR, and 3 PFR. The PFR subsequent revision data was excluded in the subcategorized Kaplan Meier analysis due to low numbers.

54 of these procedures were performed as primary CiC revisions and 31 were performed as subsequent CiC revisions (54 limbs in 54 patients with 85 CiC procedures). Nine of 54 patients did not reach 2 year follow up (range 1–20 months, mean 10 months). Only one of these nine died within the first two years after primary CiC revision. None of the 31 subsequent revision CiC cases had less than 2 year follow up.

Survival

At final follow up, 47 of 54 (87%) patients with CiC revisions had successful limb salvage and did not require an amputation (Figure 1). Thirty one of 54 (57.4%) of patients required a subsequent CiC revision of their initial CiC revision at a mean of 8.9 years post-op, with a 5-, 10-, 15-, 20- and 25-year survival of 73.7%, 51.1%, 34.3%, 12.4%, and 8.3%, respectively (Figure 2). No amputation was performed for mechanical reasons, with two for local tumor recurrence and one for infection.[9] Respective 5-, 10–15- and 20-year implant survival rates in the subsequent CiC revision cohort were 61.6%, 54.8%, 39.1%, and 19.6% (data available to 20-year survival). Ten-year overall survival of primary CiC revisions and subsequent CiC revisions were therefore similar (CI: 38%–62% vs 31%–78%, respectively), but when parsed for mechanical failures alone, 15-year survival rate was 32.5% for initial revisions and 58.5% for subsequent revisions. The mean revised MSTS functional score at final follow up was 27 (range: 14 – 30)[18].

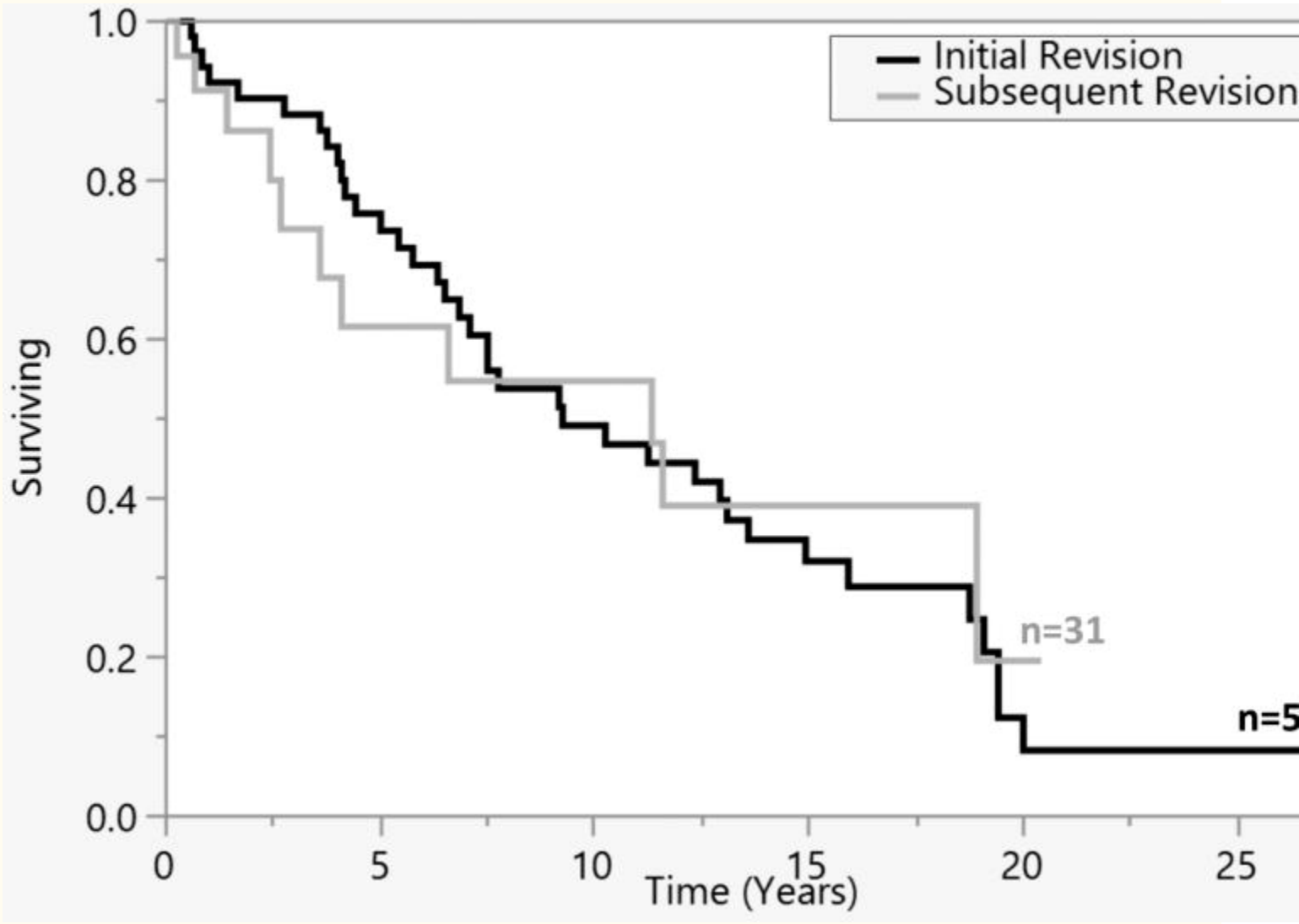


Figure 2

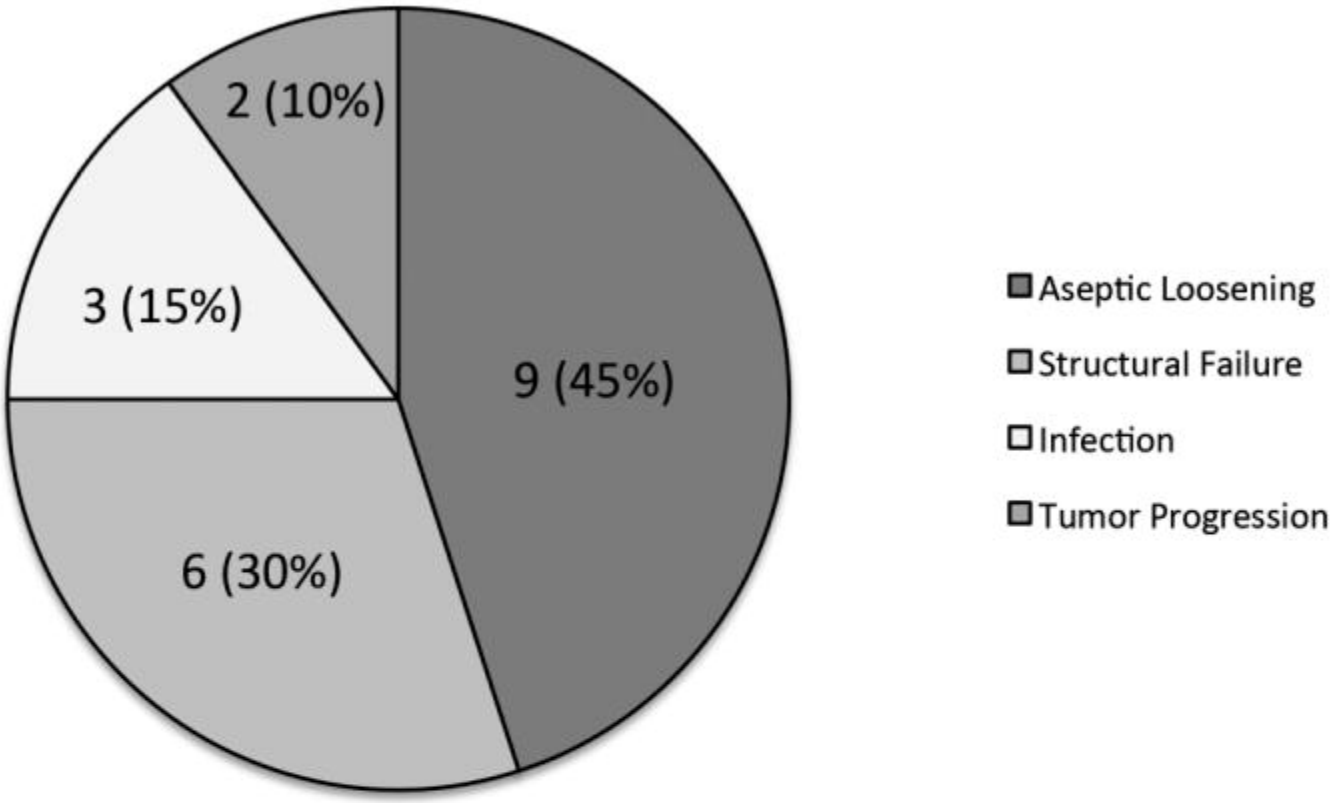
Kaplan-Meier curves that represent survival of CiC initial revisions versus subsequent revisions over a follow-up of 25 years.

Complications

Five of 54 (9%) initial CiC revisions failed due to infection. Overall complications from each revision stage are presented in Table 1. Subsequent complications based on initial failure mode are presented in Figure 3. An additional 4 of 31 (13%) subsequent CiC revisions became infected. The limb salvage rate was 87% (47/54) in this cohort.

A

Initial Failure: Aseptic Loosening



B

Initial Failure: Structural Failure

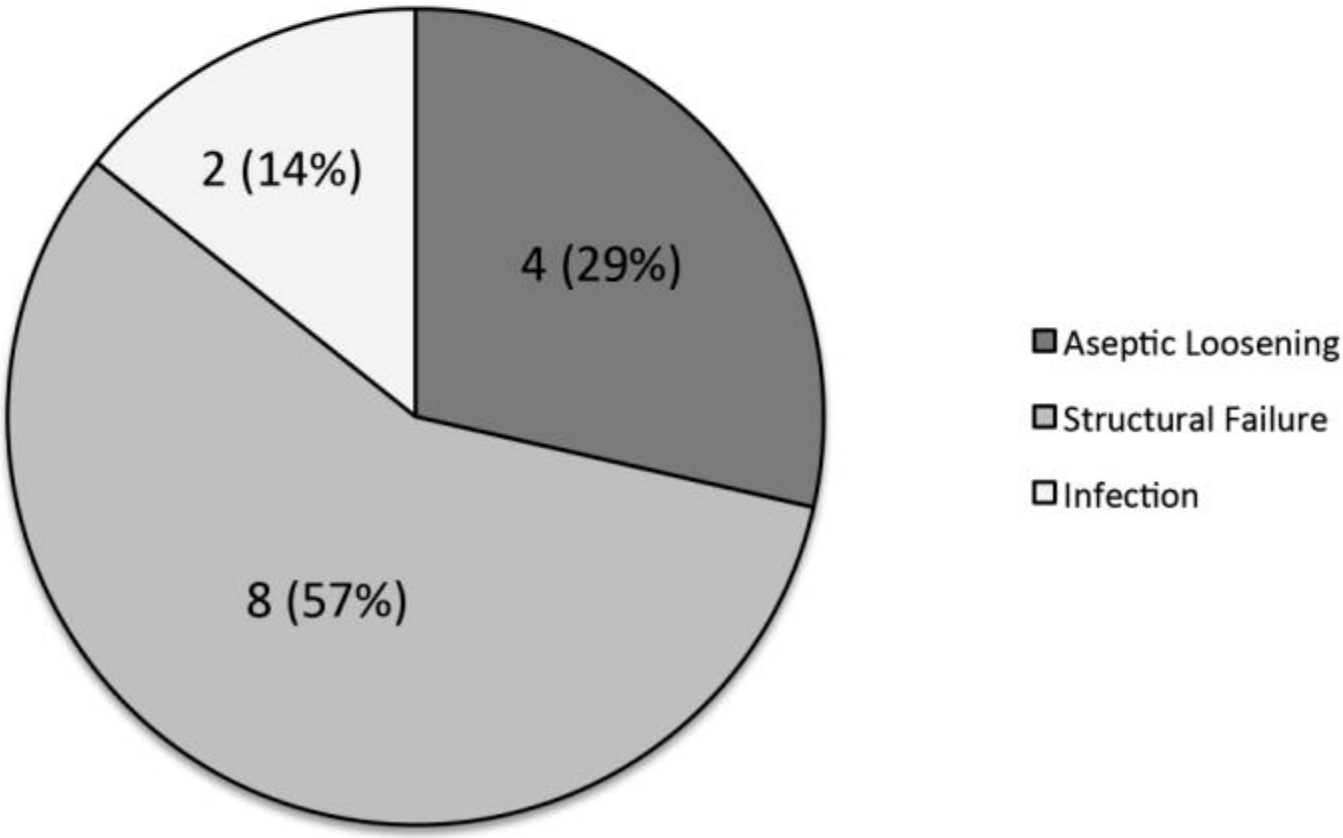


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Figure 3

Amongst initial failure modes of aseptic loosening and structural failure, frequencies of subsequent modes of failure including aseptic loosening, structural failure, infection, and tumor progression.

Table 1

Failure percentage

Modes of failure of initial and subsequent revisions across all failure types including soft tissue failures, aseptic loosening, structural failure, infection, and tumor progression. Cumulative totals tabulated in bottom line.

Failure Types	Initial (n)	%	Subsequent (n)	%
Soft tissue failure	0	0	0	0
Aseptic Loosening	29	54	13	42
Structural Failure	20	37	14	45
Infection	5	9	4	13
Tumor Progression	0	0	0	0
Total	**54**	**100**	**31**	**100**

Failure Mode

Of the 29 cases of CiC revision performed for aseptic loosening, nine (31%) were subsequently revised for aseptic loosening and six (29%) for structural failure. Of the 20 cases of CiC revision performed for structural failure, eight (40%) subsequently failed for structural failure and four (20%) eventually were revised for aseptic loosening.

Anatomic Location

In the initial revision cohort of 54 patients, there was a difference in the failure rate between anatomic location. 5-, 10-, and 15-year survival rates for DFR prostheses (n = 41) was 75.5%, 49.2%, and 29.6% respectively. 5-,

10-, and 15-year survival rates for PFR prostheses (n = 6) was 83.3%, 62.5%, and 62.5% respectively. 5- and 10-year survival rates for PTR prostheses (n = 6) was 66.6% and 22.2% respectively (Figure 4).

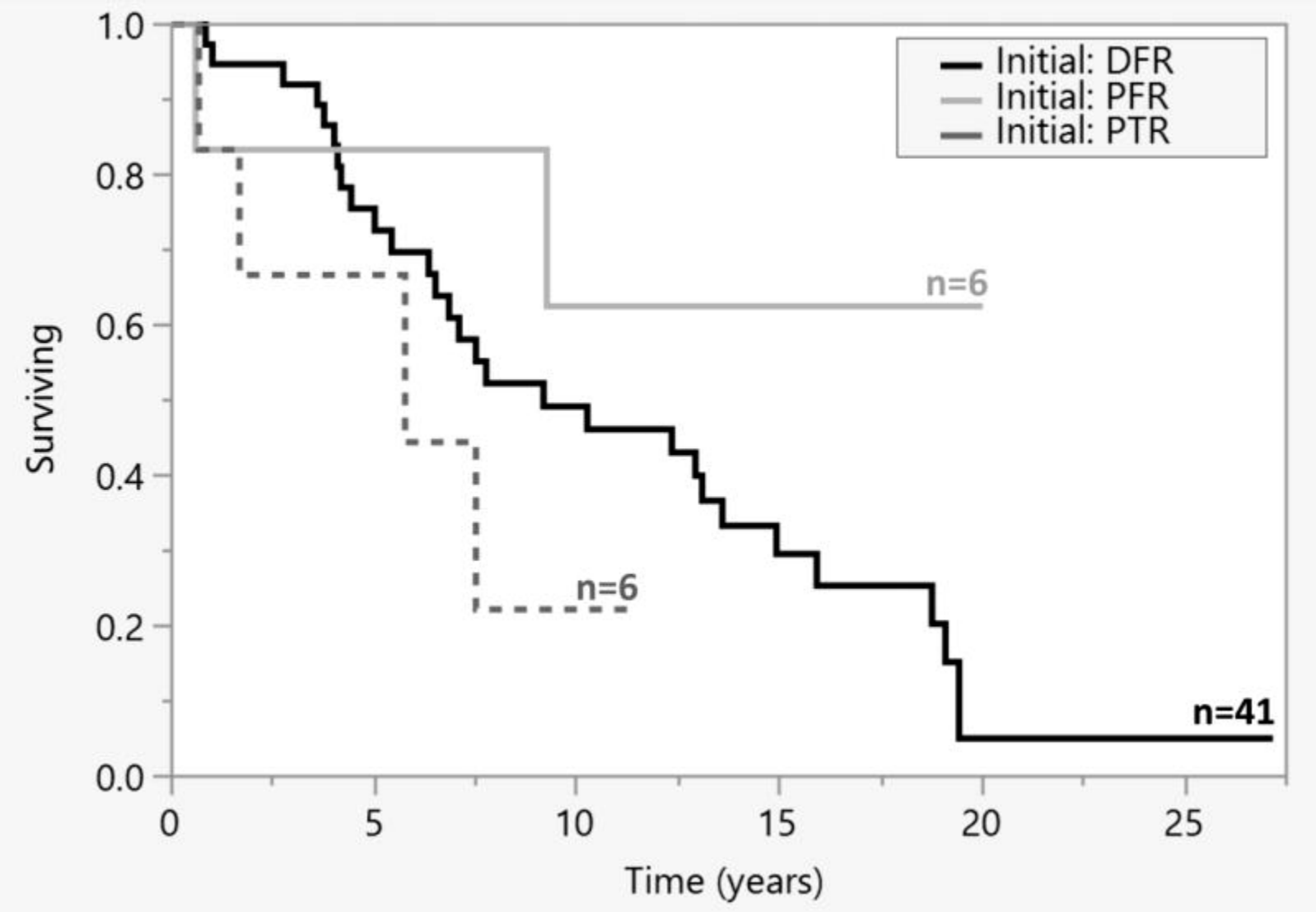

Figure 4

Kaplan-Meier curves that represent survival of CiC revisions based on location including distal femur, proximal femur, and proximal tibia. Aggregate survival of all three locations described are represented by “Initial Revision”.

Discussion

The evaluation of techniques that are able to address the problem of cemented endoprosthetic revision are increasingly important as oncologic patient survival continues to improve.[5,12,14] Unfortunately, revision endoprosthetic reconstruction remains a challenge due to concerns of insufficient remaining bone stock, poor muscle function and lack of normal soft tissue coverage. Options are extremely limited, and include conversion to a total prosthesis that spans two joints, cutting “above” the cement mantle and instrumenting native bone, a compressive osseointegration revision, and custom cross pin fixation. Working proximal to the cement mantle sacrifices bone stock and often leaves few options for subsequent complications. Unless a compatible implant was used for the primary surgery, compressive osseointegration revisions have the same requirement of Institutional Review Board approval for a custom device as custom cross pin implants, often necessitating lengthy delays for the symptomatic patient.

A CiC revision technique in this context was thought to demonstrate promise due to the fact that it is a conservative procedure that requires little to no additional bone resection, can be repeated multiple times before a higher-level reconstruction is required, and is performed with off-the shelf implants available at any time (Figure 5). However, long-term outcomes of this procedure were previously unknown. In this study, 15-year survival of CiC revision reconstruction was 34.4% and 15-year survival of a subsequent CiC revision was 39.1%, with an overall limb salvage rate of 87%. Of the 7 amputations performed, all were for tumor progression (n=2) or infection (n=5). Survival rates differed by anatomic location, but were similar across different modes of failure. Subsequent revision failures were more likely to fail by the same mechanism as the initial failure, and were also more likely to become infected.

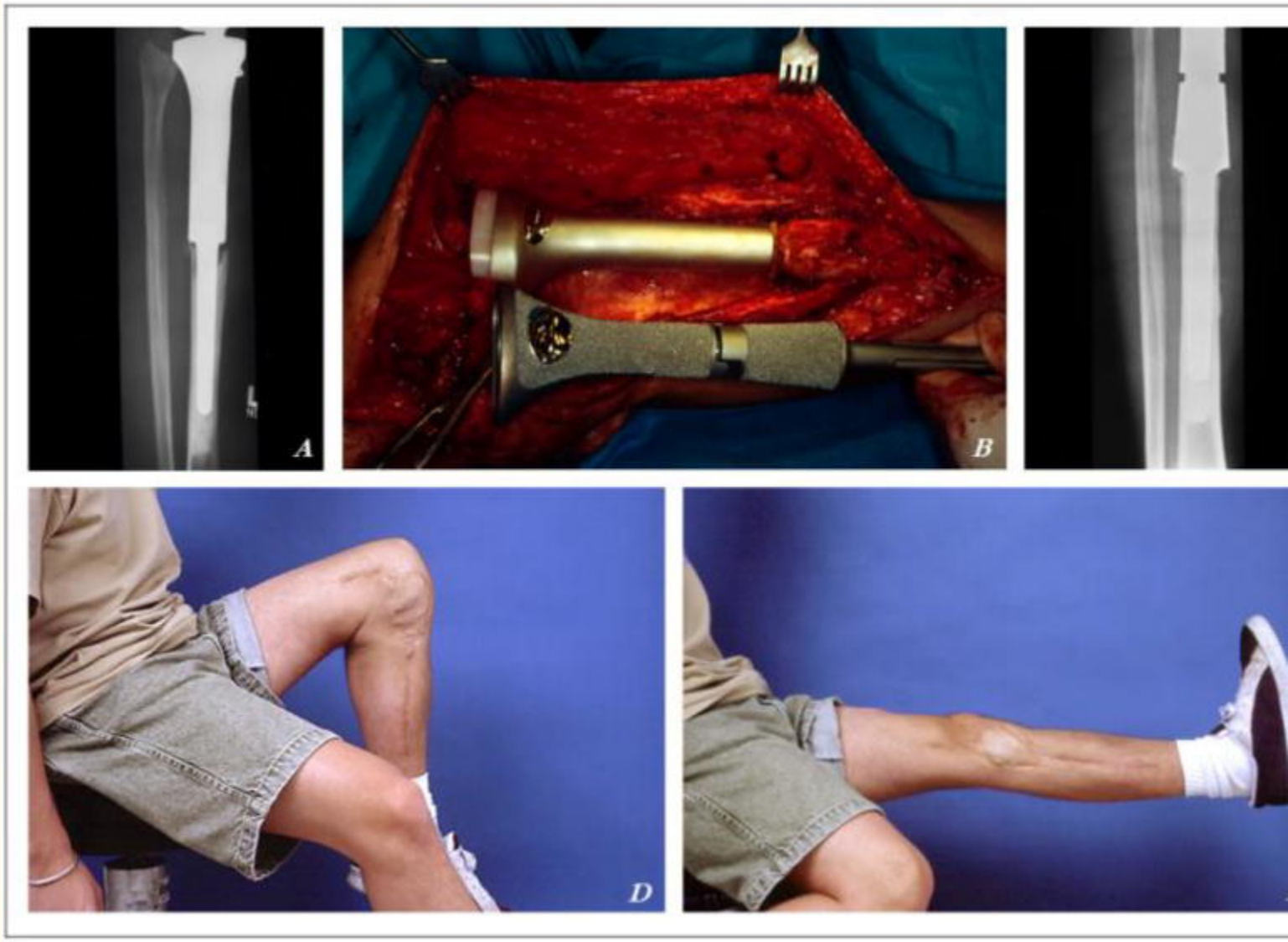

Figure 5
Representative images of cement in cement revision operative technique

A) Radiograph demonstrating proximal tibia replacement with early aseptic loosening. B) Intraoperative photo of cement in cement revision demonstrating distal femur replacement with porous extramedullary coating. C) Radiograph at 3.5-year follow-up with well-fixed implant after cement in cement revision. D–E) Long term follow-up function.

Survival

Initial and subsequent CiC revision cohorts demonstrated similar implant survival rates, and both were significantly lower than the survival rates for primary endoprosthetic reconstructions published by our group

and others.[1, 3, 4, 6, 21] This is not unexpected given the i) challenges of revision arthroplasty surgery in general and ii) the attempted conservative nature of this operation avoiding native, healthy bone. However, the fact that survival of subsequent revisions was equal to that of the initial CiC revision provides optimism in the reproducibility and durability of this technique. Nonetheless, there is no question this is a salvage technique and should be performed with tempered expectations.

When compared specifically to total femoral replacements, an alternative for a failed cemented endoprosthesis, the CiC implant survival is far more appealing. Recent literature on TFR survival demonstrates a 5-year revision-free survival of 48%, to which our 15-year data is comparable.[12] With MSTS functional scores of 24 with TFR,[22] the CiC technique appears to have superior implant survivorship and functional results. In addition, a recent study by Zimel et al. looking at compressive osseointegration fixation for DFR revision showed a 10-year implant survival rate of 74%, with a mean MSTS score for those patients who had retained their implant of 27.[23] While this series compares favorably to our results and presents an attractive option in some revision scenarios, applicability is limited due to logistic requirements. Unless the primary implant was made by the same manufacturer as the compression osseointegration implant, this revision technique necessitates Institutional Review Board and FDA approval for a custom implant, rendering it unavailable to the surgeon who requires it on a semi-urgent basis. Conversely, the CiC technique is an available off the shelf revision option regardless of manufacturer.

Complications

Based on previously published data, primary infection rate after cemented endoprosthetic reconstruction in our overall cohort of 512 patients was 2%.[21] We saw an increase in the incidence of infection at each revision intervention stage: CiC revisions failed from infection 9% of the time, subsequent revisions 13%, and tertiary revisions 55% (6/11 patients). These infection rates are comparable to published index procedure infection rates, which range greatly from 3% – 34%.[1, 3, 9, 24] Of note, our demonstrated increase in infection may be influenced by technological advances and increasing sensitivity of assays to determine infection, resulting in the identification of indolent infection cases that previously would have been declared aseptic. However, the conclusion that subsequent endoprosthesis surgery is more likely to lead to an infection is critical. We believe this conclusion highlights the appeal of the CiC revisions, as other revision strategies that use more proximal bone could jeopardize a functional amputation if the infection cannot be cleared. Other, noninfectious complication rates from the CiC technique are in line with previously published endoprostheses series, with aseptic loosening (54%) and structural failure (37%) as the most common cause for failure.[9, 10]

Forty seven of 54 (87%) patients achieved successful limb salvage using the CiC technique. We have previously shown a limb salvage rate of 81% following index procedure in this cohort,[15] and published rates from index endoprosthesis reconstruction range from 70% – 92%.[1, 3, 4] In our series, all amputations were performed for tumor recurrence or infection, in accordance with previous datasets, demonstrating the difficulty in saving the limb in these settings.[4] In our previously published cohort of 512 patients, 40% of infected prostheses and 89% of local recurrences resulted in an amputation.[5] Finally, our patients demonstrated a revised MSTS score of 27, which agrees with previous reports from our group that 64/64 patients evaluated for functional status at 13.2 years continued to be active and functional in their homes.[22] Similar studies have shown a revised MSTS score of 27 after revision DFR at 10 years follow-up.[23]

Failure Mode

In our cohort, we saw a correlation between initial failure mechanism and subsequent failure mechanism. When a patient failed for aseptic loosening or structural failure, they were more than 50% likely to fail by the same mechanism when they failed again. These findings stress the importance of life-long follow-up for these patients, enabling us to identify patients at risk of failure before their complication progresses to catastrophic status.

Anatomic Location

We saw a correlation between anatomic location of CiC revision and survival rate. In our cohort, PFR's showed highest survival rate, followed by DFR then PTR. Of note, numbers of patients were small in PFR and PTR groups (n=6), so the reader should interpret these findings accordingly. However, these findings agree with

other authors, who have demonstrated that tibia prostheses required the highest revision rate of any anatomic location, (46%) and higher than DFR (10%).[1] Finally, the Henderson series demonstrated worse overall survival in the combined DFR-PTR and PTR groups at 15 – 30 years, which is in concordance with our findings of a decreased survival rate for PTR.[9] We find that our PTR patients have more challenging soft tissue environments, especially in the revision setting, which provides a rationale for these findings.

Limitations

This study has a number of limitations, including its retrospective design and lack of a control group. Both of these limitations are difficult to overcome considering first the rarity of musculoskeletal tumors, and the smaller number of those that required a revision after endoprosthetic reconstruction. We are able to compare our results to historical controls as a frame of reference, but no direct comparison with another reconstruction technique can be made. The limited power of the study is further diminished when we stratify by anatomic location. Nonetheless, we believe the trend toward better survival for PFR>DFR>PTR CiC is worth noting, especially as it mirrors existing trends in primary reconstructions.[21]

Conclusions

At long term follow up, endoprostheses revised with the CiC technique showed consistent 15-year survival from initial (34%) to subsequent (39%) revision. We showed that the CiC technique is a repeatable, conservative procedure in these challenging patients. While we expect a significant complication rate from this procedure, including an increasing risk of infection, we also expect to be able to repeat these surgeries for the life of the patient with a reasonable chance of maintaining a well-functioning limb.

In considering cemented endoprostheses and the CiC revision technique for treatment of musculoskeletal malignancy, it is crucial to emphasize that these patients are patients for life. The success of this procedure, defined as avoidance of amputation or TFR, depends critically on prompt recognition and treatment of loosening and impending fracture. In our practice, we have a very low threshold for radiographic evaluation and subsequent surgical exploration in any patient with symptomatic thigh pain that is not resolved with a 2-week period of rest, crutches and anti-inflammatories. Future directions for this work should include a prospective controlled study, directly comparing the survival of the CiC technique to comparable revision options. In conclusion, despite a relatively high failure rate, results of CiC revisions demonstrate that this technique can address a challenging problem with reproducible rates of success.

Synopsis

The Cement in Cement (CiC) technique for revision of cemented endoprostheses is a technically demanding solution to a challenging clinical problem. At long term follow up, endoprostheses revised with the CiC technique showed consistent 15-year survival from initial (34%) to subsequent (44%) revision. While we expect a significant complication rate from this procedure, including an increasing risk of infection, we also expect to be able to repeat these surgeries for the life of the patient with a reasonable chance of saving their limb.

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Footnotes

Disclosures: The remaining authors certify that he or she have no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.