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RESEARCH ARTICLE

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What are the indications and survivorship of tumor endoprosthetic reconstructions for patients with extremity metastatic bone disease?

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Abstract

Background and Objectives: Given advances in therapies, endoprosthetic reconstruction (EPR) in metastatic bone disease (MBD) may be increasingly indicated. The objectives were to review the indications, and implant and patient survivorship in patients undergoing EPR for MBD.

Methods: A review of patients undergoing EPR for extremity MBD between 1992 and 2022 at two centers was performed. Surgical data, implant survival, patient survival, and implant failure modes were examined.

Results: One hundred fifteen patients were included with a median follow-up of 14.9 months (95% confidence interval [CI]: 9.2–19.3) and survival of 19.4 months (95% CI: 13.6–26.1). The most common diagnosis was renal cell carcinoma (34/115, 29.6%) and the most common location was proximal femur (43/115, 37.4%). Indications included: actualized fracture (58/115, 50.4%), impending fracture (30/115, 26.1%), and failed fixation (27/115, 23.5%). Implant failure was uncommon (10/115, 8.7%). Patients undergoing EPR for failed fixation were more likely to have renal or lung cancer ($p = 0.006$).

Conclusions: EPRs were performed most frequently for renal cell carcinoma and in patients with a relatively favorable survival. EPR was indicated for failed previous fixation in 23.5% of cases, emphasizing the importance of predictive survival modeling. EPR can be a reliable and durable surgical option for patients with MBD.

KEYWORDS

bone neoplasms, endoprostheses, metastasis, orthopedic surgery

1 | INTRODUCTION

Metastatic bone disease (MBD) is heterogeneous in presentation due to inherent variability in the systemic behavior of primary cancer types and their corresponding impact on the bone tumor environment. While bone destruction and subsequent impending or actualized pathologic fracture is a common manifestation of MBD, patient survival, and skeletal response to modern treatments is largely dependent on tumor biology. Contemporary surgical decision making in MBD must incorporate several factors including patient goals, estimated patient survival, potential for local therapeutic response and both anatomic and fracture characteristics.[1] Structural goals include providing a thoughtful surgical intervention that will ultimately outlive the patient's projected survival.[2,3] Traditional stabilization techniques including intramedullary nail fixation (IMN), and open reduction and internal fixation (ORIF) have a large role in the management of MBD fractures, with formal tumor en bloc resection and endoprosthetic reconstruction (EPR) being reserved for specific clinical scenarios.[4] EPR in MBD is traditionally indicated for cases of solitary metastatic or oligometastatic disease, in patients with favorable survival, patients with extensive bone loss precluding adequate fixation, or failed previous conventional fixation (Figure 1).[5,6] EPR has many distinct advantages over fixation, such as facilitating a single definitive surgery, early mobilization and weight bearing, and potentially minimizing repeat trips to the operating room due to implant failure.[5,7,8] Before the transition from custom to modular tumor endoprosthetics with more reliable modern designs,[9] EPR use was limited in MBD patients due to lack of off the shelf availability and length of fabrication.

Patient survival estimates are important when considering implant choice. Advances in cancer therapies such as targeted treatments and immunotherapies have resulted in improved patient survival for certain cancer types such as advanced renal cell carcinoma and non-small cell lung cancer.[10,11] While survival in patients with MBD requiring orthopedic surgery has shown unclear temporal trends,[12] a recent study of femoral metastasis secondary to renal and lung carcinoma demonstrated measurable impact of biologic anti-neoplastic agents on patient survival.[13] In general, the orthopedic oncology community has placed greater consideration on the benefits of en bloc resection and EPR for appendicular MBD in the appropriate clinical scenario.[13–16]

Using a large retrospective dataset, we asked (1) what are the indications for tumor EPR in patients with MBD from two tertiary bone oncology centers, including distribution of primary histology, (2) what are the implant survivorship and modes of failure in this patient population, and (3) what characteristics are associated with failure of surgical fixation requiring revision surgery with EPR?

2 | MATERIALS AND METHODS

2.1 | Study design and setting

We performed a multicenter retrospective review of patients undergoing EPR for MBD from 1992 to 2022. Sites included were the University of California, Los Angeles and the University of Calgary. Patient data extracted included age, sex, primary diagnosis, procedure performed, concomitant use of therapies targeting driver mutations (targeted therapies) or immunotherapy, indication for surgery, implants utilized, implant survival and patient survival when available. EPRs were performed by four fellowship trained orthopedic oncology surgeons (S.K.T.P., M.J.M., J.J.E., N.M.B.).

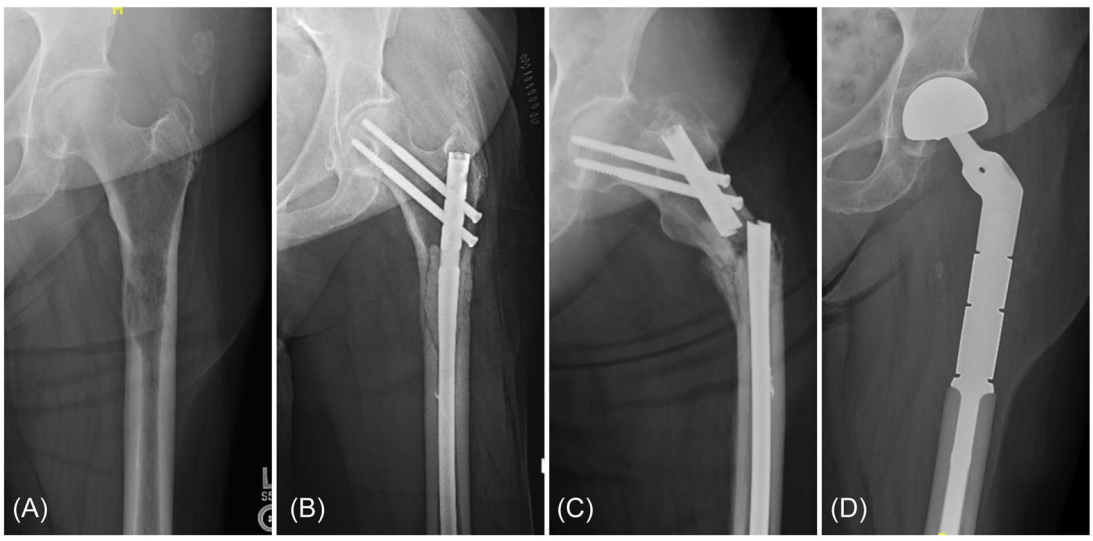

FIGURE 1 Endoprosthetic reconstruction after intramedullary nail implant failure performed for renal cell carcinoma. (A) Lytic subtrochanteric metastatic deposit was initially managed with debulking, cementation and intramedullary nail fixation (B). Eight months later the patient developed an intraprosthetic fracture (C) and ultimately underwent implant removal and proximal femoral replacement (D).

2.2 | Surgical interventions

Patients were included in this study if they underwent EPR for an MBD indication. Indications for EPR were coded for all patients, and were categorized into actualized pathologic fractures, impending pathologic fractures, and EPR for failed previous surgical fixation. Those defined as failed previous surgical fixation had their index operation for MBD, and failed secondary to progressive symptomatic metastatic disease with or without implant failure or periprosthetic fracture. Patients who underwent primary EPR for actualized or impending pathologic fractures were categorized as "primary EPR". Implant failure modes were classified by the Henderson classification, which includes five types of failure (broadly categorized into mechanical or non-mechanical), with nonmechanical failures identified as requiring removal or revision of the endoprosthesis stemmed components.[17] Mechanical failures are divided in Type 1 (soft-tissue failure), Type 2 (aseptic loosening), and Type 3 (structural failure). Nonmechanical failures are divided into Type 4 (infection necessitating removal of device) and Type 5 (tumor progression or recurrence).

2.3 | Other data sources

Use of immunotherapy and targeted therapies was factored into analysis for patients with sensitive primary cancers (renal cell, lung, and melanoma). Immunotherapy was approved for use in 2015 by the FDA and Health Canada, and therefore cases treated after the year 2015 were included for assessment of frequency of immunotherapy use in patients who were undergoing EPR for failed previous surgical fixation.[18] PathFx v3.0 (https://www.pathfx.org) was utilized as a retrospective audit of predicted patient survival in patients who failed previous surgical fixation.[19,20]

2.4 | Statistical analysis

Descriptive statistics were used to summarize demographic and surgical variables. Categorical variables were analyzed using a chi-square (χ^2) test. Implant survival and overall patient survival and was calculated using the Kaplan–Meier survival analysis and associated 95% confidence intervals (CIs). Statistics were conducted using GraphPad Prism 9 and Stata (Release 16; StataCorp LLC).

2.5 | Ethics approval

Retrospective database review was performed under ethics approval from the UCLA institutional review board (IRB) at UCLA, under IRB protocol #10-001857, and the University of Calgary Research Ethics board/Health Research Ethics Boards of Alberta Cancer Committee (REB20-0335).

3 | RESULTS

3.1 | Patient demographics

A total of 115 patients were included with a mean age of 60.6 (SD 14.7) and 59 (51.3%) were female (Table 1). Ninety patients were included from the University of California, Los Angeles (dates ranging 1992–2022), and 25 patients were included from the University of Calgary (dates ranging 2007–2021). Median patient follow-up was 14.9 months (95% CI: 9.2–19.3). The three most common primary

TABLE 1 Demographic and clinical variables for patients undergoing endoprosthetic reconstruction for metastatic bone disease.

Variables	*N* (%)
Age	60.6 (SD 14.7)
Sex	
Male	56 (48.7)
Female	59 (51.3)
Primary diagnosis	
Breast	26 (22.6)
HCC	5 (4.3)
Lung	16 (13.9)
Melanoma	4 (3.5)
Other	13 (11.3)
Prostate	4 (3.5)
Renal	34 (29.6)
Sarcoma	8 (7.0)
Thyroid	3 (2.6)
Unknown	2 (1.7)
Procedure	
PHR	41 (35.7)
RTSA	4 (3.5)
DHR	7 (6.1)
PFR	43 (37.4)
DFR	20 (17.4)
TFR	4 (3.5)
Implant manufacturer	
Depuy-Synthes	25 (21.7)
Onkos	1 (0.9)
Stryker/Howmedica	58 (50.4)
Techmedica	1 (0.9)
Zimmer-Biomet	30 (26.1)

Abbreviations: DFR, distal femur replacement; DHR, distal humerus replacement; PFR, proximal femur replacement; PHR, proximal humerus replacement; TFR, total femur replacement.

malignancies were renal cell (34/115, 29.6%), breast (26/115, 22.6%), and lung (16/115, 13.9%). Patients with MBD underwent EPR for three indications: actualized pathologic fracture (58/115, 50.4%), impending pathologic fracture (30/115, 26.1%), and failed surgical fixation (27/115, 23.5%).

3.2 | Implant and surgical characteristics

The most common EPR was proximal femur replacement (PFR; 43/115, 37.4%), followed by proximal humerus replacement (PHR; 41/115, 35.7%), distal femur replacement (DFR; 20/115, 17.4%), distal humerus replacement (DHR; 7/115, 6.1%), and total femur replacement (TFR; 4/115, 3.5%) (Table 1). In the PHR group, four reverse total shoulder EPRs were performed from 2020 onwards. Implant manufacturer breakdown can be found in Table 1, with the three most common manufacturers being Stryker/Howmedica (58/115, 50.4%), Zimmer-Biomet (30/115, 26.1%), and Depuy-Synthes (25/115, 21.7%).

3.3 | Implant and patient survival

Implant failure was identified in 10 patients in this cohort (8.7%) (Table 2).[17] The 1-year implant survival statistic was 82.1% (95% CI: 67.3–90.6) (Figure 2A). Median patient survival was 19.4 months (95% CI: 13.6–26.1) (Figure 2B). Of the 10 patients that experienced implant failure, 3 were EPRs done for the indication of failed surgical fixation. Soft-tissue failure (Type 1) was the most common mode of failure (4/10, all cases of wound dehiscence) followed by tumor recurrence/local progression (Type 5) (3/10). There were two structural failures (Type 3), and two infections necessitating implant removal (Type 4). One implant failed in >1 Henderson mode (Type 3 and Type 4). When stratified by anatomic location, two PHRs (one rTSA), two PFRs, two DFRs, two DHRs, and two TFRs failed.

3.4 | EPRs for failed previous surgical fixation

We identified 27 patients in this series that underwent EPR for failed previous surgical fixation. Primary surgical fixation consisted of 4 (14.8%) cases of hemiarthroplasty, 13 IMN (48.2%), and 10 ORIF (37%). Of the 27 conversions to EPR, there were 15 PFRs (55.6%), 5 PHRs (18.5%), 3 DHRs (11.1%), 3 TFRs (11.1%), and 1 DFR (3.7%) performed. The three most common cancer types in this cohort were renal cell (11/27, 40.7% vs. 26.1% primary EPR), lung (7/27, 25.9% vs. 10.2% primary EPR) and breast (6/27, 22.2% vs. 22.7% primary EPR). Patients undergoing EPR for failed fixation were more likely to have a primary diagnosis of renal or lung carcinoma, in comparison to those undergoing primary EPR ($p = 0.006$) (Figure 3). Eight patients underwent EPR for failed fixation with a diagnosis of renal or lung carcinoma after the year 2015; 87.5% (7/8) had a documented history of concomitant immune checkpoint blockade (6/8, 75%) and/or targeted therapy (1 patient on monotherapy sunitinib) (Table S1). Patient estimated survival was retrospectively predicted at the time of initial surgical fixation with data available for 12 patients (Figure 4; Table S2). Estimated 1-month mean survival for this cohort was 89.6% (range: 81%–97%, SD 5.9), with 57.8% (range: 32%–84%, SD 17.1) at 3 months, 42.6% (range: 15%–74%, SD 18.3) at 6 months and 36.2% (range: 11%–67%, SD 17.1) at 1 year.

TABLE 2 Implant failure by Henderson mode.

Mode of failure[a]	
Total	10 patients
Type 1 (soft tissue failure)	4
Type 2 (aseptic loosening)	0
Type 3 (structural failure)	2
Type 4 (infection)	2
Type 5 (tumor progression)	3

[a]One patient had >1 mode of failure.

4 | DISCUSSION

The musculoskeletal oncology community identified delineating the role of en bloc resection and reconstruction versus stabilization in MBD as a top research priority in orthopedic oncology.[21] Tumor EPRs for MBD may be an increasingly valuable tool over conventional fixation methods in the oncology surgeon's clinical decision-making process as patient survival for various cancer subtypes improves.[13] In this study a multicenter database review of patients undergoing en bloc resection and tumor EPR for extremity MBD was performed. The most common primary histologies in this series were renal cell carcinoma, breast cancer and lung cancer, which is consistent with previous series' assessing EPR in MBD.[5,6] In comparison to a historic cohort at UCLA (1980–2003), EPRs were more commonly performed in patients with lung cancer (13.9% in this study vs. 5.4% in historic cohort).[7] Actualized pathologic fracture was the most common surgical indication for EPR (consistent with published data on proximal femur EPR for MBD),[22] followed closely by impending fracture and failed surgical fixation. PFRs and PHRs were the two most common endoprosthetics employed in this dataset, and implant longevity was favorable and greatly exceeded patient survival. Ten (8.7%) patients required reoperation for EPR failure with soft tissue failures (all wound dehiscence) encompassing the most common mode of failure. Janssen et al. performed a large review of surgically managed proximal femoral metastases comparison outcomes and durability of IMN, ORIF, and EPR (including long stem hemiarthroplasty).[22] In that study, systemic complications between strategies were no different. However, 13% of patients underwent additional fixation after ORIF, compared to 0 patients in the EPR group, further emphasizing the mechanical durability of EPRs for MBD patients.

In comparison to the patients who underwent primary EPR, patients that failed previous fixation were more likely to have a

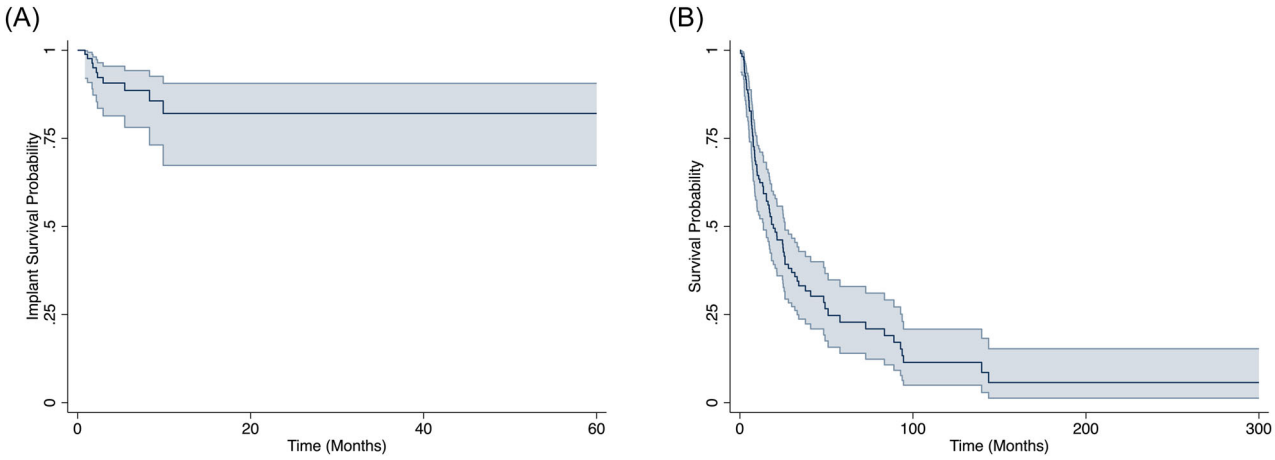

FIGURE 2 Kaplan–Meier survival estimates performed for (A) implant survival and (B) overall patient survival. Shaded areas represent a 95% confidence interval.

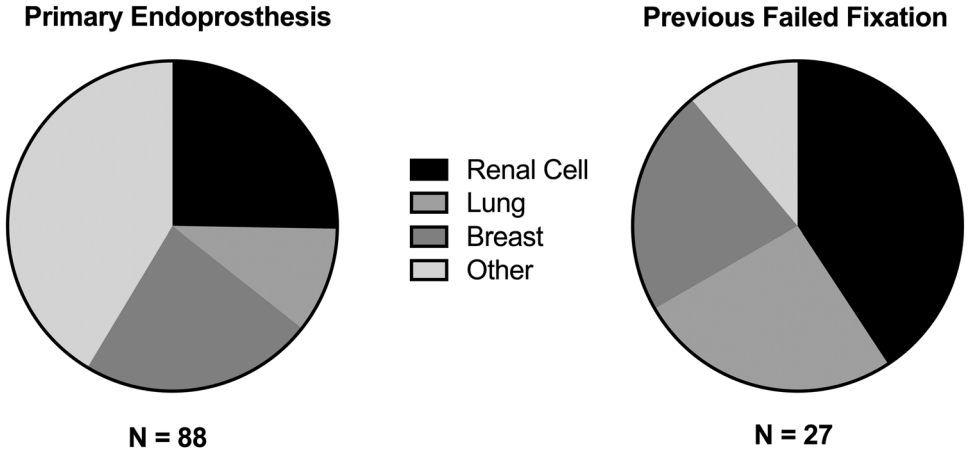

FIGURE 3 Primary tumor type distribution for those undergoing endoprosthetic reconstruction for the indication of failed previous surgical fixation and those undergoing primary endoprosthesis. "Other" tumor types summarized in Table 1.

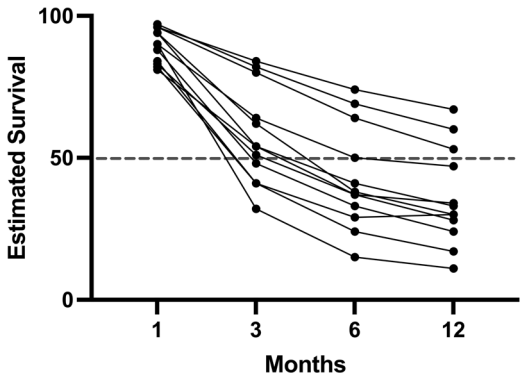

FIGURE 4 PathFx v3.0 survival estimates at the time of surgical fixation for patients who ultimately required endoprosthetic reconstruction for failure of fixation. Of 12 patients, 4 had an estimated survival of ≥50% at 6 months, demarcated by the dashed line.

diagnosis of renal or lung carcinoma (66.7% and 36.4%, respectively). IMN was the most common primary surgical procedure in this group, followed by ORIF and hemiarthroplasty, and the proximal femur was the most common location for conversion to EPR. Advances in targeted therapies and immunotherapies will continue to alter the landscape of patient survival in MBD, particularly for patients with currently sensitive histologies such as renal cell carcinoma and non-small cell lung carcinoma.[13] Most patients who out-lived conventional fixation implants since 2015 were being actively treated with immune checkpoint blockade and/or targeted therapies (7/8 patients). Recent research efforts have aimed at delineating discrepancies between systemic and osseous response to novel cancer therapies, with some data suggesting this discrepancy may be attributed to the unique osseous immune microenvironment.[23–25] This presents an important consideration for surgical planning in patients that appreciate improved survival but have progressive MBD despite otherwise successful systemic treatment. Notably, a survey

of the musculoskeletal oncology society members determined that a >6 months predicted survival helps determine surgical management of proximal femur MBD to favor PFR over IMN.[26] This survey further delineated that those surgeons with more than 10 years of clinical experience were more likely to recommend PFR for breast cancer MBD scenarios versus surgeons with less than 10 years of experience, whereas both groups more commonly recommended PFR in renal cell cancer scenarios.

In a large systematic review of survival in patients undergoing surgery for appendicular MBD, 1-year combined survival across 67 studies was 41%; 1-year survival for breast cancer cases was 53% versus 66% for renal cancer and 41% for lung cancer.[12] Median patient survival in our study was 19.4 months, and implant durability was much greater than patient survival. Patients who outlived fixation implants underwent subsequent EPR. In a subset with available data (12 patients who previously failed fixation), estimated survival at time of initial surgical fixation was 89.6% at 1 month, with a drop to 42.6% at 6 months and 36.2% at 1 year. 1/3 of the three of the estimates provided a 6-month survival prediction of ≥50%, which theoretically may have aided initial surgical decision making to favor primary EPR for those patients. As new iterations of survival algorithms emerge, they must continue to follow trends in overall survival particularly in those with primary cancers that respond to novel cancer therapies.[27]

There are limitations to this study in addition to the inherent biases of being a retrospective data capture. As both centers included are tertiary musculoskeletal oncology centers, there is a possibility of referral bias. Cases included spanned multiple decades from 1992 to 2022, which is both a strength of the study as well as a limitation due to more recent advances in therapies and advances in implant design and evolving surgical indications. We did not include a matched cohort of patients who underwent surgical fixation which did not allow for a matched comparison; however, this was not suited to the scope of our clinical questions.

5 | CONCLUSIONS

The role of en bloc resection and EPR in patients with MBD is a top priority in orthopedic oncology. These data provide an updated analysis of the indications, outcomes, and complications in patients with MBD undergoing EPR. When compared to fixation techniques and when done for the appropriate indication, EPR provides a reliable and durable surgical reconstruction that will likely last beyond the duration of the patient's life. Those undergoing EPR for failed surgical fixation were more likely to have a diagnosis of renal cell or lung cancer.

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CONFLICT OF INTEREST STATEMENT

Nicholas M. Bernthal has or may receive payments or benefits from the National Institutes of Health. Nicholas M. Bernthal is also a consultant for Zimmer Biomet and Onkos. Shannon K. T. Puloski is a consultant for Depuy-Synthes and has received research funding for unrelated work. Alexander B. Christ is a consultant for Smith and Nephew and Onkos. Other authors decalre no conflict of interest.

DATA AVAILABILITY STATEMENT

NA.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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