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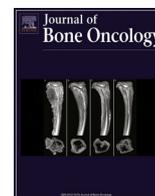
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Intramedullary rod failure in metastatic breast cancer: Do triple negative cancer patients have more revision surgery?



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ABSTRACT

Background: Breast cancer is the most common cancer and second cause of death in women worldwide. Patients with breast cancer are classified into subgroups based on the presence or absence of hormone receptors and the human epidermal growth factor 2-neu (HER-2) marker, the different molecular profiles come with an associated prognosis and variety of possible treatment options. Patients with triple negative cancer have a worse prognosis, a more aggressive behavior, higher likelihood of spreading, a higher risk of recurrence and a poorer outcome overall. Intramedullary rod fixation has proven to provide a good outcome and function in patients with metastatic breast cancer, but no study has addressed the receptor-status potential outcome differences that may affect disease progression at an orthopaedic surgery site. **Questions/Purposes:** (1) Do patients with triple negative breast cancer have a higher revision rate of intramedullary rod fixation of bone metastases? (2) Do patients with metastatic triple negative breast cancer have a higher revision rate of intramedullary rod fixation due to local disease progression?

Methods: This was a single-center, observational, retrospective cohort study. Fifty-seven patients with a diagnosis of breast cancer metastatic to long bones who underwent surgical fixation with an intramedullary rod for a pathological fracture or an impending fracture due to a bone metastasis with a Mirels' score equal or above 8 between January 2004 and December 2016 at our institution were included. All implants used were from the same manufacturer (Stryker Corp., Mahwah, NJ, USA). Patients were divided into two groups based on the receptor status of the tumor and were classified either as triple negative, when the tumor lacked progesterone, estrogen and HER-2 receptors, or as receptor-positive when the presence of one or a combination of either three was proven. In the triple-negative tumor group the mean follow up time was 26 months (SD 29) and median follow up time was 16 months. In the receptor-positive tumor group mean follow up was 27 months (SD 24) with a median follow up of 19 months. To assess possible associations between different factors and the outcomes of interest, we used either the chi-square test or Fisher's exact test for categorical variables and the ANOVA test for continuous variables. For the survival assessment, a Kaplan-Meier analysis was performed and for the cumulative incidence a competing risk analysis was utilized.

Results: The intramedullary rod revision rate for patients in the triple-negative tumor group was 17%, while for the receptor-positive group it was 12%, this was not statistically different for our sample size. The mean time for revision of the intramedullary rod in the whole sample was 19 months (SD 11, range 6–40). The causes of revision were disease progression (43%), nonunion (29%) and surgeon error (29%). The cumulative incidence of revision surgery was 6% (CI 95%, 2–14%) at 12 months and 20% (CI 95%, 8–36%) at 60 months.

Conclusions: Intramedullary rodding can be considered for the treatment of long bones metastases in breast cancer patients for an impending or actual pathological fracture. There is no difference in the intramedullary rod revision rate among patients with different receptor-status when comparing triple-negative tumor patients and receptor-positive ones.

Level of Evidence: Level III, therapeutic study.

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1. Introduction

Breast cancer is the most common cancer and second cause of death in women worldwide [1,2]. It is estimated that in 2019 there will be more than 260,000 new cases in the United States [3]. The incidence has remained stable for Caucasian women but has slightly increased for African American women [3]. Bone is the most common site of disease spread, and the factors associated with it are well known [4]. Breast cancer is very heterogeneous with different molecular profiles; patients are divided into subgroups based on the presence or absence of hormone receptors and the human epidermal growth factor 2-neu (HER-2) marker [5,6]. Depending on the receptor-status, patients have different therapeutic options and prognosis. The most common breast cancer subtypes are estrogen or progesterone receptor positive [7]. Tumors with absence of these three receptors, progesterone, estrogen and HER-2, are known as triple-negative cancers. This status is more frequent among young women and African Americans [8,9]. Patients with triple negative tumors have fewer therapeutic options, besides cytotoxic chemotherapy [10]. Additionally, those patients with a triple negative cancer have a worse prognosis as these tumors appear to have a more aggressive behavior, with higher likelihood of spreading, a higher risk of recurrence and a poorer outcome overall [11–14].

Disease spread limited to the skeletal system is associated to better prognosis when compared to the presence of visceral metastases [15,16]. Patients with bone metastases despite the better prognosis, are prone to skeletal related events (SRE) that require medical and/or surgical interventions. SRE are associated with pain, pathologic fractures, spinal cord and/or nerve compression and hypercalcemia and are a significant source of morbidity for these patients [17]. Bisphosphonates have been shown to reduce the risk of developing SRE, delay the median time to an SRE, and appear to reduce bone pain when compared to placebo or no bisphosphonate [18].

Previous studies have demonstrated a good outcome and function with intramedullary rod fixation for long bone impending or pathologic fractures in metastatic cancer patients [19–21]. To the best of our knowledge no previous studies have specifically focused on breast cancer receptor-status, with its different behaviors, disease progression risks, prognosis and treatment options, and its potential effect on implant survival.

We therefore asked: (1) Do patients with triple negative breast cancer have a higher revision rate of intramedullary rod fixation of bone metastases? (2) Do patients with metastatic triple negative breast cancer have a higher revision rate of intramedullary rod fixation due to local disease progression?

2. Patients and methods

2.1. Description of experiment, treatment, or surgery

This was a single-center, observational, retrospective cohort study. In our surgical database we identified patients with a diagnosis of breast cancer metastatic to long bones who underwent surgical fixation with an intramedullary rod between January 2004 and December 2016 at our institution. Patients with a breast tumor other than an adenocarcinoma, such as phyllodes, sarcoma or lymphoma among others, were not included. Additionally, patients with other types of implant, such as endoprosthesis or plates and screw osteosynthesis, either as a single fixation method or in addition to an intramedullary rod in the index procedure, were excluded from the analysis as well. All operations were performed by fellowship-trained surgeons at a tertiary center in patients with a pathology proven diagnosis. Patients were recom-

mended for the surgical procedure either due a pathological fracture of a long bone, defined as a cortex breach with or without displacement, where a metastatic lesion was observed, or an impending fracture due to a bone metastasis in a long bone, but no actual cortex fissure, in patients with a Mirels' score equal or above 8 [22]. Lesions in the proximal or distal third with severe bone destruction that precluded nail end-fixation were indicated for an endoprosthesis replacement, and not included in this analysis. Cement augmentation was added at the surgeon's preference. All implants used were from the same manufacturer (Stryker Corp., Mahwah, NJ, USA). Immediately after the surgical procedure all patients were allowed to bear weight in the operated extremity as tolerated. For the upper extremity procedures, a sling was occasionally prescribed for comfort and for the lower extremity nails, crutches or walkers were recommended at the physical therapist's discretion.

Operative reports, clinic notes, and radiographs were analyzed. Patients were followed for a minimum of 24 months or until death or revision surgery was performed.

More than 300 records of patients treated by the oncology orthopedic service during the study period were reviewed. Of these, 57 met the inclusion criteria and were submitted to analysis (Fig. 1). The patients were divided into two groups based on the receptor status of the tumor and were classified either as triple negative, when the tumor lacked progesterone, estrogen and HER-2 receptors, or as receptor-positive when the presence of one or a combination of either three was proven. Six patients were included in the triple-negative tumor group and the remaining 51, who had at least one receptor present, were added to the receptor-positive group.

In the triple-negative tumor group the mean follow up time was 26 months (SD 29) and median follow up time was 16 months. In the receptor-positive tumor group mean follow up was 27 months (SD 24) with a median follow up of 19 months. The mean follow up times among groups were not found to be different for this sample size. Three patients died in the triple-negative tumor group and fourteen died in the receptor-positive one.

2.2. Variables, outcome measures, data sources, and bias

Demographic information as well as receptor status, treatments received, surgery indication and type of implant utilized were recorded. In addition, plain radiographs were reviewed by two fellowship-trained oncology orthopedists. There were no conflicting opinions regarding the failure diagnoses. The rod was considered to have failed when a surgical revision procedure was required either due to hardware mechanical failure, disease progression, surgeon error (i.e., inappropriate implant choice or surgical technique error), or non-union of a fracture.

Patient demographics at presentation were compared among the two groups (Table 1). All patients in our cohort were female. The mean age in our full cohort was 59 years old (range 31–89 years). All patients had pathology proven metastatic breast adenocarcinoma.

In the triple-negative tumor group, the mean age was 62 (SD 12, range 47–77), for our second group, with the receptor-positive tumors, the mean age was 59 (SD 12, range 31–89). The age distribution among groups was found not different for our sample size. Regarding the surgically treated lesion location, in the triple-negative tumor group 67% (4 of 6) had a humeral lesion that required rodding, for the remaining of the group, it was a femoral lesion (2 of 6). In the receptor-positive group 65% had a femoral metastatic lesion (33 of 51) and 35% had a humeral located lesion (18 of 51). The location distribution was not different for the sample size. In the triple-negative tumor group, 33% of the patients (2 of 6) had an actual fracture, while the remaining 67% had an

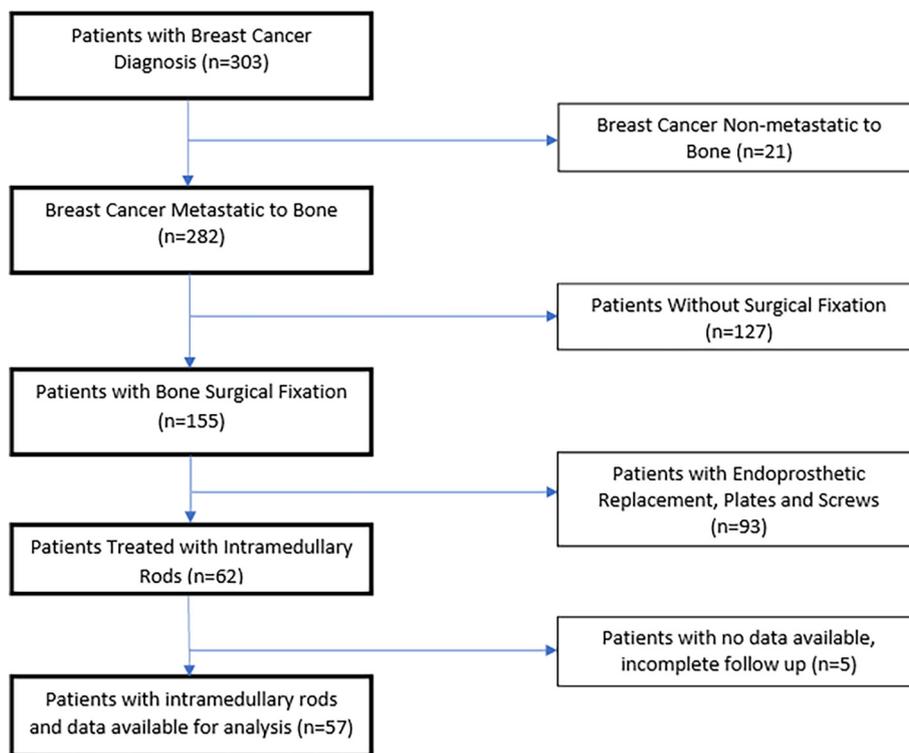


Fig. 1. Chart depicting the STROBE patient selection flow chart used in our sample, showing a total recruited n = 62 and total available for analysis n = 57.

Table 1
Table depicting the different patients' demographic characteristics per group.

Characteristic	Receptor-Positive Group (n = 51)	Triple-Negative Tumor Group (n = 6)
Female:Male	51:0	6:0
Mean Age	59	62
Nail Location	Humerus - 18 Femur - 33	Humerus- 4 Femur- 2
Fracture vs. Impending	Fracture - 17 Impending - 34	Fracture - 2 Impending - 4
Nail type	Cephalomedullary - 28 Intrameduallary - 23	Cephalomedullary - 2 Intrameduallary - 4
Cement Augmentation	Yes - 9 No - 42	Yes - 2 No - 4
Systemic Treatment	Hormonal - 32 Chemotherapy - 6 Targeted - 5 Combination- 3 None - 5	Hormonal - 2 Chemotherapy - 2 Targeted - 0 Combination - 0 None - 2
Radiotherapy	Preoperatively - 8 Postoperatively - 22 None - 21	Preoperatively - 0 Postoperatively - 3 None - 3
Antiresorptive Drugs	Biphosphonates - 22 Denosumab - 4 None - 25	Biphosphonates - 2 Denosumab - 0 None - 4
Multiorgan Metastases	Exclusive Bone - 11 Visceral Metastases - 40	Exclusive Bone - 1 Visceral Metastases - 5
Median Karnofsky score	70	75

impending fracture (4 of 6). In the other group, also 33% had an actual fracture (17 of 51), and 67% had an impending fracture (34 of 51). Likewise, distribution was not different for the sample size. In both groups, all patients with humeral lesions, had an intramedullary type of nail, while for the patients with femoral lesions, those with a proximal third location but no extension to the femoral neck or head, had a cephalomedullary type of nail inserted. Patients with a mid-diaphysis metastatic lesion, received an intra-

medullary type of nail. In our sample, no patient had a lesion distal enough to require a retrograde nail, all nails inserted in both groups were in anterograde fashion. In the triple-negative tumor group, 33% had a cephalomedullary rod inserted (2 of 6), the remaining patients in this group had all humeral lesions, with an intramedullary humeral device utilized for fixation. In the receptor-positive tumor group, 55% (28 of 51) had a cephalomedullary type of rod, 45% (23 of 51) had an intramedullary nail, this included all the humerus lesion patients (18 patients) and 5 intramedullary femoral nails. The type of fixation device distribution was not different for our sample size. In the triple-negative group 33% (2 of 6) had cement augmentation added to the rod fixation, both patients had surgery for fixation of a humeral lesion. In the other group, 18% (9 of 51) had cement augmentation added during the nail fixation procedure for either humeral or femoral lesions. This distribution was not different among the two groups for our sample size.

From the breast cancer standpoint, 83% (5 of 6) in the triple-negative group had multiorgan disease spread, including lung, liver and/or brain, besides the bone lesions. In the receptor-positive group, 78% (40 of 51) had disease spread to multiples sites other than bone. The remaining of patients in both groups, had only bone metastatic disease without any evidence of visceral secondary lesions. No difference was found for this distribution for our sample size. For the patients' performance status the Karnofsky scale was used [23]. In the triple-negative tumor group, 50% (3 of 6) had a scale of 80 (able to carry normal activity with effort) and the remaining 50% (3 of 6) had a scale of 70 (cares for self, unable to carry normal activity). In the receptor-positive group, 37% (19 of 51) had a scale of 70 and 29% (15 of 51) had a scale of 80, the range for this group was 50-90 and values other than 70 or 80 were present in smaller percentages (Table 2). The distribution for the Karnofsky scale among the two groups was not found to be different for our sample size. In terms of antiresorptive therapy, in the triple-negative tumor group, 33% (2 of 6) were receiving bisphos-

Table 2

Table depicting the revision patients' demographic characteristics.

Patient	Receptor-status	Location	Fracture	Failure Type	Time to Revision	Treatment
47, F	Receptor +	Femur	No	Disease Progression	26	Curettage + Cement
51, F	Receptor +	Femur	No	Disease Progression	22	Amputation
52, F	Receptor +	Femur	No	Surgical error	40	Rod Exchange
77, F	Triple Negative	Humerus	No	Disease Progression	12	Distal Humerus Replacement
59, F	Receptor +	Humerus	Yes	Nonunion	8	Rod Exchange
62, F	Receptor +	Femur	Yes	Surgical error	6	Rod Exchange
59, F	Receptor +	Femur	Yes	Nonunion	22	Rod Exchange

Time to Revision in months, F = Female.

phonate treatment at the time of the surgical procedure, the remaining 67% (4 of 6) were not taking any antiresorptive drugs. In the receptor-positive group, 43% (22 of 51) were taking bisphosphonates and 8% (4 of 51) were receiving denosumab as antiresorptive treatment, the remaining 49% (25 of 51) were not receiving any antiresorptive drugs at the time of the surgical procedure or previously. Two patients in the receptor-positive group who were receiving bisphosphonates had jaw osteonecrosis as a treatment related complication. This distribution was not different for our sample size. Three patients (50%) had radiation to the lesion after the surgical procedure in the triple-negative tumor group and the remaining three (50%) of that same group did not receive any radiation at all. In the receptor-positive group 16% (8 of 51) had radiation therapy prior to the surgical procedure, 43% (22 of 51) received it postoperatively and the remaining 41% (21 of 51) did not receive radiotherapy at all. The radiotherapy distribution among the two groups was not found to be different for our sample size. In the triple-negative tumor group 33% (2 of 6) were receiving systemic chemotherapy, 33% (2 of 6) were receiving hormonal therapy; these patients initially had a hormone-positive tumors but were discovered to have changed to a triple-negative cancer when a biopsy during the rodding surgical procedure was obtained; and the remaining 33% (2 of 6) was not receiving any treatment since the breast cancer was diagnosed with the biopsy from the rodding surgery. In the receptor-positive group 63% (32 of 51) were receiving hormonal therapy, 12% (6 of 51) were on chemotherapy, 10% (5 of 51) were under targeted therapy, 6% (3 of 51) were receiving a combination of either chemotherapy and targeted therapy (one patient), or chemotherapy and hormone therapy (one patient) or targeted and hormone therapy (one patient). Five patients in this group were not receiving any systemic oncologic treatment, in four of them the breast cancer was diagnosed with the biopsy obtained during the intramedullary rod surgery and the other fifth patient refused any form of systemic treatment. No patient of any group was receiving immunotherapy.

Our primary study endpoint was surgical revision of the intramedullary rod, and we assessed the different rates in the group with triple-negative tumors and the one with receptor-positive tumors. We tested this by comparing the cumulative incidence of our endpoint in the two different groups. Among the groups the surgical indications were identical; patients with a pathology proven diagnosis of breast adenocarcinoma metastatic to long bone with either a pathological fracture of a long bone where a metastatic lesion was observed or an impending fracture due to a bone metastasis in a long bone with a Mirels' score equal or above 8. Additionally, implants from the exact manufacturer (Stryker Corp., Mahwah, NJ, USA) were used in both groups as well.

Our second study question was the incidence of intramedullary rod revision specifically due to disease progression, compared among our two groups, one only with triple-negative tumors and thus less systemic treatment options and worse prognosis associated, and the other group with receptor-positive tumors and a wider

array of systemic treatment options available as well as a more benign prognosis. Failure of the implant leading to revision due to disease progression was defined as an increase in the metastatic lesion area observed on radiographic images of the bone in question and compared to the same radiographic images at the time of the initial surgery causing the implant to mechanically fail (break) or causing enough symptoms, such as increasing pain or inability to bear weight, to warrant the surgeon to proceed with a revision prior to the actual mechanical failure of the rod. This was tested by comparing the different incidence of intramedullary rod revision due to disease progression among the different groups.

Additionally, the intramedullary rod revision cumulative incidence in metastatic breast cancer patients was assessed through a competing risk analysis with death as a competing event. Moreover, the patients' overall survival was determined by a Kaplan-Meier analysis and the difference in survival among the two groups was assessed by a log-rank test.

2.3. Statistical analysis, study size

We performed statistical analyses with SPSS Statistical Software, version 25.0 (IBM Inc., Armonk, NY, USA) and for the competing risk analysis we utilized R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). To assess possible associations between different factors and the outcomes of interest, we used either the chi-square test or Fisher's exact test for categorical variables and the ANOVA test for continuous variables. For the survival assessment, a Kaplan-Meier analysis was performed and for the cumulative incidence a competing risk analysis was utilized. All tests were deemed significant if p was < 0.05 .

3. Results

The intramedullary rod revision rate for patients in the triple-negative tumor group was 17% (1 of 6). In the receptor-positive group the revision rate of intramedullary devices was 12% (6 of 51). Despite the rate being smaller in the receptor-positive group this was not significantly different for the sample size. The mean time for revision of the intramedullary rod in the whole sample was 19 months (SD 11, range 6–40).

Among the patients who underwent a revision of the intramedullary nail ($n = 7$), three had the initial surgery indicated for an actual pathological fracture, while the remaining four had the initial rod fixation for an impending fracture in a symptomatic patient with a Mirels' score equal or above 8 (Table 2). This distribution was not different for the sample size. Additionally, among these same patients who needed a revision surgery, only one had cement augmentation, while the other six did not and this was not statistically different. Five patients had surgery for a metastatic lesion in the femur, while the remaining two had a humerus lesion. The anatomical location distribution was not different for our sample size.

The odds ratio of a patient with a triple-negative tumor with an intramedullary rod fixation of a metastatic lesion to necessitate a revision of the implant compared to those patients in the receptor-positive group in the same situation is OR = 1.5, CI 95% 0.15–15.11; this was not statistically different.

Two patients in the receptor-positive group (2 of 51) needed a revision of the intramedullary rod due to progression of the disease, while that was the cause for revision in only one patient in the triple-negative tumor group (1 of 6). This distribution was not different for our sample size.

Among all the patients that required a revision procedure, the most frequent cause was disease progression with 43% (3 of 7), followed by nonunion in 29% (2 of 7) and surgeon error in the same frequency, 29% (2 of 7) (Table 2). Of the patients with a nonunion, one had radiotherapy prior to the procedure and the second patient refused radiation treatment. Regarding the failures cate-

gorized as surgical error, those included the absence of distal rod fixation and suboptimal positioning; the later initially performed at an outside institution.

In the group of patients who required a revision of the intramedullary rod (n = 7), six were receiving hormonal therapy at the time of the revision and the seventh one refused any systemic treatment and died soon after. Two of the patients received radiation to the lesion surgically fixated prior to the initial surgery, three did it after the intramedullary rod was in place and two refused radiotherapy. Four of the seven patients were receiving bisphosphonates, none was receiving denosumab and three were not taking any antiresorptive drugs. None of these factors showed a difference in affecting the revision outcome for our sample size.

In a competing risk analysis with death of the patient as the competing event, the cumulative incidence of revision surgery

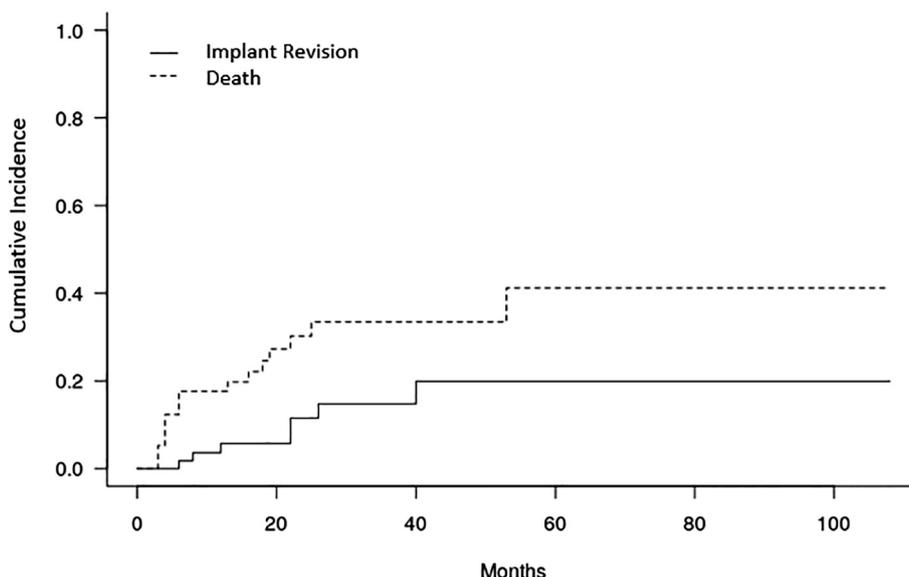


Fig. 2. The cumulative incidence of revision surgery with death of the patient as a competing risk.

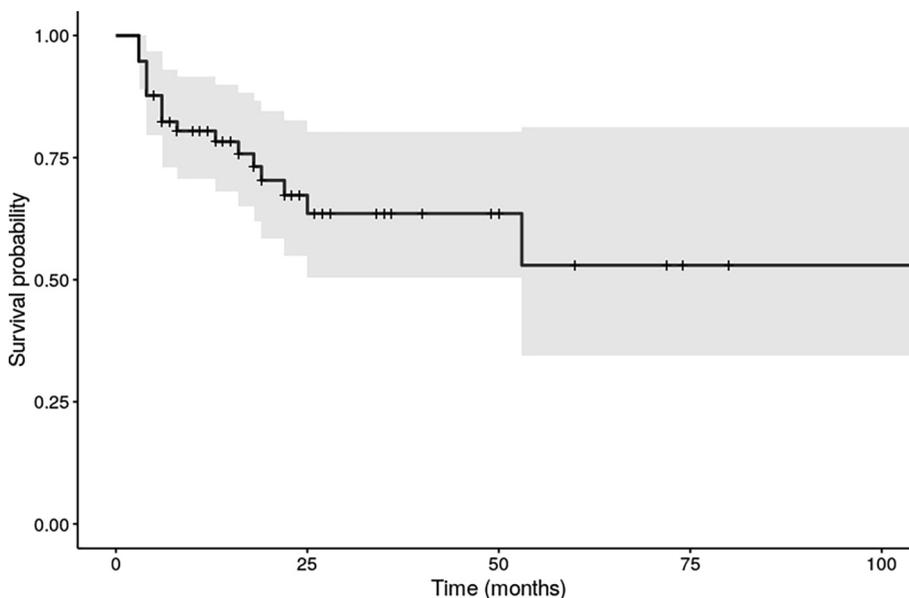


Fig. 3. Kaplan-Meier analysis of the overall patient survival with CI95%.

was 6% (CI 95%, 2–14%) at 12 months and 20% (CI 95%, 8–36%) at 60 months (Fig. 2).

With the Kaplan–Meier analysis, the overall patient survival was 81% (CI 95%, 70–92%) at 12 months and 53% (CI 95%, 35–81%) at 60 months (Fig. 3). The survival was not different when comparing among groups for our sample size.

4. Discussion

Breast Cancer is the most common cancer affecting women, about eighty percent of these patients will develop bone metastases at some point in their disease course and this is the most common site for secondary disease spread [4,1]. Advances in treatment options, which now include hormonal therapy, chemotherapy, targeted therapy and immunotherapy, have taken the 5-year survival rate to 89% currently in the United States, with the main cause of death remaining the distant lesions [24]. Unfortunately, despite all these improvements, triple-negative tumors continue to be considered the most aggressive subgroup with fewer treatment possibilities [25,26]. This subgroup accounts for 15% of the breast cancer diagnoses and is known for its heterogeneity, aggressive evolution and higher risk of recurrences [10]. No prior study has addressed if this behavior difference would also affect the survival of intramedullary rodding; a common treatment option for bone metastases that do not require resection; in these patients. Osseous spreading puts in action a vicious cycle involving osteoclast interaction with cancer cells and its concurrent activation, leading to pathological bone destruction and fractures [27]. Long-lasting bone fixation is paramount in these patients who now are living longer to maintain mobility and a good quality of life [4]. Additionally, it is of high importance for the treating oncology orthopedist to understand the differences in behavior, prognosis and adjuvant treatment response in the different breast cancer subgroups. In our study we found an overall revision rate of the intramedullary rods of 12%, with a higher rate (17%) in the triple-negative tumor subgroup compared to the receptor-positive section of the sample (12%). Moreover, our data suggests that the overall cumulative incidence of revision surgery was 6% at the first year from the index surgery and 20% at 5 years from the initial procedure, which may be higher in the future as patients survive longer with better systemic treatment. Previous literature demonstrated that hormone-receptor positive patients have a higher risk of having bone metastatic disease, but concomitantly these same patients also tend to have a better prognosis, with better treatment response and longer overall survival [9,28,29,13,14]. Earlier studies have shown that the most important factor for bone fixation failure was the length of the patient's survival [30,31]. In accordance with this, our data showed that patients with metastatic breast cancer treated with intramedullary rods required a late revision with a mean time for the revision procedure of 19.4 months. This suggests surgeons should be cognizant of the fact that their fixation may need to outlive the initial 6-month interval. Additionally, our study showed a higher rate of femur nail failure (14%, 5 of 35) compared to humerus nail failure (9%, 2 of 22), that difference was not significant for our sample size, but may be a reflection of different frequency of failure modes for upper extremity (non-weightbearing) devices compared to lower extremity ones. Prior studies have shown that humerus nail failure rates can be up to 10% due to non-union, whereas femur nails can undergo mechanical failure with implant breakage in up to 16% with an important percentage of those (41%) occurring in patients treated for a pathological fracture [32,33].

One might expect that fixation in triple negative disease patients would require more revisions due to progression of triple negative disease locally at the site of fixation. However this was not seen likely due to the fact that with local progression also comes significant systemic progression of triple negative disease

that leads to the passing of the patient. Aggressive systemic progression allows for the local fixation to outlast the patient's life expectancy. In the future as treatments become better and lead to longer life expectancy one will likely see a higher revision rate that might suggest a different index surgical procedure should be performed, i.e., either segmental replacement or arthroplasty.

Surprisingly, this study also showed that although radiation oncologists routinely recommend postoperative radiation to the surgical site post-fixation this is not always accomplished. Typically, radiation is delivered locally to minimize disease progression at the operative fixation site and thus to prevent future hardware failure. Our study indicated that not all the patients received radiation at the fixation site. Those who were not irradiated presented no more risk for fixation failure than the patients who did receive radiotherapy to the affected bone. This is may be due to the novel superior treatment options involving targeted therapy and newer chemotherapy alternatives. Further studies will be needed to better elucidate this phenomenon. These patients may benefit from a multidisciplinary breast cancer team that should include discussions with the orthopaedic surgeon or orthopaedic oncologist. An additional unexpected finding was that only 51% of the patients (29 of 57) included in the study were receiving antiresorptive bone therapy at the time of the fracture or previously. Bone metastases present with an imbalance between bone resorption and bone remodeling, favoring the former. Bisphosphonates have a proven role in altering this phenomenon and preventing fractures and other SREs; members of the multidisciplinary treating team must be mindful of this [18].

5. Limitations

This study had a number of limitations. First, our sample was of a relatively reduced size, with a total of 57 patients, and even though this was the biggest sample we found in the literature regarding specifically metastatic breast cancer and its treatment exclusively with intramedullary rodding, we acknowledge we did not have enough power to achieve significance in our results [30,20]. For the difference in revision rate among the different groups, 12% vs. 17%, our study attained to show a trend in the association between hormone receptors and rod survival, unfortunately those numbers did not reach statistical significance and our sample size likely played a role in that. For such rate difference, our study would have needed a sample of over 1500 patients and for such specific scenario that would entail a multicentric study. Secondly, we may have incurred in a selection bias, including patients who in addition of the intramedullary rodding underwent excision of the metastatic lesion by means of curettage and cementing. By excising the secondary focus of disease, those patients would have had a lower risk of revision due to disease progression, but our results showed that the distribution of these patients was not different among the two groups nor did it affect the revision outcome. Additionally, among the patients who did not need a revision or died, the triple -negative tumor group had a higher percentage of patients not seen in the past 5 years (17%, 1 of 6), compared to the receptor-positive group (8%, 4 in 51). While this may be considered as a retention bias our analysis showed that this distribution was not different for our sample size. Furthermore, regarding the number of deaths in each group, those were also not different for the number available. Our institution is the only National Cancer Institute (NCI)-designated Comprehensive Cancer Centers in the state, as such we have patients coming from long distances who eventually continue their follow up locally, in such circumstances we acknowledge that we could have underestimated the overall rod revision rate. Fourthly, cancer patients may present with a compromised performance status, and those bedridden or with limited activity may have a lower risk of experiencing rod failure symp-

toms. Nevertheless, any potential performance bias, was reduced by taking the Karnofsky score of our patients into our analysis. The Karnofsky score is a performance scale which assesses patients according to their functionality with a prognostic implication. The median Karnofsky score was not different among the two groups, 75 for the triple-negative tumor group and 70 for the receptor-positive group. Additionally, the systemic treatment and radiotherapy exposure was also not different among the groups; thus, the average effect of activity level on the rod survival was probably not different as well. Our study showed that most of these patients had multiorgan metastatic disease (79%) nonetheless presented with a good performance status, with 49% of the patients having a Karnofsky score equal or above 80 (able to carry on normal activity and to work) and 88% with a score equal or above 70 (able to live at home and care for most personal needs), emphasizing again the importance of providing good long-lasting bone fixation. An additional limitation of our study is the lack of information regarding the bone density status of the patients. Previous studies have demonstrated that breast cancer patients due to treatment induced ovarian failure are at risk for decreased bone density and this may have potentially played a role in implant failure [34]. Lastly, we only utilized implants from the same manufacturer, which could also be considered a strength of our study since by doing so we reduced other confounding variables, but correspondingly by doing so our results may not extrapolate to implants produced by other manufacturers which may have different results in this same scenario. We also acknowledge that not all the patients received postoperative radiation as would be recommended in this scenario; nonetheless our data suggests that there was no increased risk to nail failure in the absence of postoperative radiotherapy.

6. Conclusions

Intramedullary rodding can be considered for the treatment of long bone metastases in breast cancer patients in the setting of an impending or actual pathological fracture. There is no difference in the intramedullary rod revision rate among patients with different receptor-status when comparing triple-negative tumor patients and receptor-positive ones. Diligent attention to the longer expected survival of these patients, especially those with bone as the sole site of spread, and the late failure time is recommended and should be taken into account when making treatment decisions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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