Prognostic factors in patients with breast cancer metastasis in the femur treated surgically

Guilherme Grisi Mouraria, Silvia Raquel Frick Matte, Carlos Hideo Hanasilo, Maria Julia Rosso de Carvalho, Mauricio Etchebehere

University of Campinas, Unicamp, Medical School, Department of Orthopedics, Campinas, SP, Brazil

BACKGROUND: Breast carcinoma is a common malignancy in the developed world. Late diagnosis of the disease is associated with bone metastasis. The femur is commonly affected. Prognostic factors of mortality in patients with bone metastases originating from cancers in general have been reported. However, there is no specific report of prognostic factors in relation to breast cancer metastasis in the surgically treated femur. The determination of prognostic factors in patients with bone metastasis can assist in therapeutic decisions.

OBJECTIVE: To determine clinical and orthopedic factors related to mortality in patients with breast cancer and metastases to the femur treated surgically.

METHOD: This was a retrospective study and included 41 patients undergoing surgical treatment of femoral metastases. We analyzed the following variables: (i) number and location of bone metastases, (ii) visceral metastases, (iii) presence of pathological fracture, (iv) fixation method, and (v) laboratory tests. These factors were correlated with mortality using Cox Multivariate Logistic regression and Kaplan-Meier curves.

RESULTS: There was a high prevalence of multiple metastases associated with pathological fractures at the time of surgery. Mortality was high and early. Subtrochanteric location, the presence of fractures, anemia, and alterations in renal function were associated with higher mortality. The fixation method, the number of bone metastases, and the presence of metastasis in other organs did not affect mortality.

CONCLUSIONS: Breast cancer with metastasis to the femur is an advanced disease with early mortality. Clinical and orthopedic factors should be considered. Surgery is recommended when lesions occur, regardless of the type of implant used.

KEYWORDS: Breast Cancer; Femur Metastasis; Prognosis; Mortality.
the lesions, in the femur was divided into proximal (transstrochanteric region and femoral neck), subtrochanteric region, distal, and diaphysis. The clinical parameters studied were serum hemoglobin (Hb) levels, serum creatinine (Cr) and urea (Ur) values, as well as the presence of metastasis in other organs. The staging of the tumor in relation to parenchymal and/or visceral metastasis was performed with the aid of computed tomography or MRI. We calculated the correlation of mortality with these preoperative variables using Cox multivariate logistic regression model. We also calculated survival curves with censored data by the Kaplan–Meier method (tested by a log-Rank method, with \( p < 0.05 \) as the limit for significance).

**RESULTS**

Patient follow-up ranged from 8 to 63 months (average, 37 months). One patient was lost to follow-up. The mean age was 53.8 years. The average number of bone metastases, including the femur, was 10.8. The proximal femur proved to be the most common location of bone metastases and fractures. Most of the patients (30) had pathological fracture at the time of surgery. Clinical variables evaluated were the preoperative values of Cr and Ur (for renal function) and serum Hb. On average, the values were within normal limits. The presence of at least one visceral/parenchymal metastasis (most commonly a pulmonary metastasis) associated with the bone metastasis was detected in 24 patients (58%).

In the surgical treatment of bone metastases, femoral prosthetic replacement and syntheses (intramedullary nails or plates) were typically used.

Mortality was 70% (29 patients), primarily in the first year after surgery. The median survival was 8.1 ± 6.6 months as illustrated in Fig. 1. The location of the lesion, the presence of fractures, and clinical variables (Creatinine and Hemoglobin) were correlated with mortality. However, treatment method, presence of metastases in visceral organs, and the number of bone metastases were not, as shown in Table 1.

For statistical purposes, the subtrochanteric region was used as a reference. The presence of metastasis in this region increased mortality by 3- to 3.3-fold in comparison to those located in the proximal femur and diaphysis, respectively (Table 1). Figure 2 shows the distribution of mortality according to the location of the femoral lesion.

![Kaplan-Meyer curve for overall mortality](image)

**Figure 1** - Kaplan-Meyer curve for overall mortality. The median survival was 8.1 months, with 70% of deaths occurring during the first year after surgery.

**Table 1** - Mortality estimates obtained by Cox multivariate logistic regression

<table>
<thead>
<tr>
<th>Variables</th>
<th>regression coefficient</th>
<th>hazard ratio (HR)</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>proximal(1)</td>
<td>−1.088</td>
<td>2.969(2)</td>
<td>1.010 - 4.929</td>
<td>0.050</td>
</tr>
<tr>
<td>diaphysis</td>
<td>−1.20</td>
<td>3.322(2)</td>
<td>1.362 - 5.820</td>
<td>0.050</td>
</tr>
<tr>
<td>distal</td>
<td>−0.443</td>
<td>1.557(2)</td>
<td>−0.462 - 3.517</td>
<td>0.610</td>
</tr>
<tr>
<td>−0.233</td>
<td>1.265(3)</td>
<td>0.697 - 5.232</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>−0.026</td>
<td>1.026</td>
<td>0.934 - 1.968</td>
<td>0.090</td>
<td></td>
</tr>
<tr>
<td>1.295</td>
<td>3.650(4)</td>
<td>1.690 - 5.610</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>1.14</td>
<td>3.130</td>
<td>1.170 - 5.060</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>1.010</td>
<td>0.910</td>
<td>−0.101 - 2.900</td>
<td>0.987</td>
<td></td>
</tr>
</tbody>
</table>

(1) neck and transtrochanteric region of femur; (2) HR subtrochanteric reference; (3) HR with a drop 1 mg/dl of hemoglobin; (4) HR with an increase 1 mg/dl of creatine.
Clinical data showed that a 1 mg/dL increase in serum Creatinine was associated with about a 3.6-fold increased risk of death (Table 1). Creatinine values above 1.2 mg/dL also increased mortality (Fig. 3A). Urea levels did not appear to affect mortality.

A drop in the hemoglobin value of 1 mg/dL increased the risk of death by approximately 1.2 fold (Table 1). In patients with Hb < 11 mg/dL, mortality was significantly increased (Fig. 3B).

The presence of fractures was associated with increased mortality, especially in the first 12 months postoperatively (Table 1). However, after 24 months, there was no statistical difference in mortality (Fig. 4).

Mortality was not influenced by the number of bone metastases or the presence of multiple lesions (Table 1, Fig. 5B). Moreover, the presence of metastasis in other organs was not associated with increased mortality (Table 1, Fig. 5A). The type of procedure performed (osteosynthesis or arthroplasty) did not affect mortality (Table 1, Fig. 6).

**DISCUSSION**

Metastasis of breast cancer to the femur requires, in most cases, surgical intervention because conservative treatments and radiotherapy are not effective in preventing pathological fractures. The study population had advanced neoplasia, because the presence of bone metastasis indicates disseminated disease in stage IV. The average age here was 56 years, lower than that reported in the literature1.

The average number of bone metastases at the time of treatment of a femoral lesion was high, so there was a tendency to also find metastasis elsewhere, an observation consistent with the literature2. In this series, femoral metastasis was associated with lesions in other organs in 58% of cases, an indicator of advanced disease. Thus, the staging of the disease is important because there is a high likelihood of finding other bone lesions and/or metastases in other organs at the time of diagnosis of a femoral lesion. These factors are important in preoperative planning and overall treatment of the disease.

In terms of topographic distribution, the femoral lesions were predominantly located in the proximal region, which is consistent with published reports3. The proximal location of the lesion results in a higher probability of fracture due to
mechanical forces acting on the hip. Additionally, a proximal lesion more often needs prosthetic replacement, reflecting an increase in the duration of the surgery and its complications, thereby increasing mortality. However, in this study, the subtrochanteric region resulted in worse prognosis, in contrast to reported data. This difference may be due to the fact that other reports considered this region to be part of the proximal femur. Thus, differentiation between lesions in the subtrochanteric proximal, intertrochanteric, and neck regions is important because of different associated mortalities. Thus, a subtrochanteric location, which is associated with reduced survival, may be treated with palliative procedures and, eventually, minimally invasive procedures to improve the quality of life.

In our study, the type of surgery (osteosynthesis or prosthetic replacement) had no effect on mortality. This divergence from the literature may be due to the surgeon’s level of expertise with arthroplasty. In the literature, fixation was associated with a greater chance of implant failure and revision surgery. These techniques should therefore be used in patients with reduced life expectancies. Prosthetic replacements should be reserved for patients with a better prognosis due to the reduced possibility of implant failure.

Fractures were associated with high mortality in the first 12 postoperative months (Fig. 5), in agreement with the literature. Fractures caused increased mortality due to restriction to bed rest and associated complications. Prophylactic treatment of bone lesions can result in shorter hospital stay and reduced blood loss during surgery, leading to lower mortality. Fractures associated with bone metastasis of breast cancer have higher mortality than do other cancers, such as those of the lung or kidney.

Clinically, renal function parameters and hemoglobin levels were, on average, normal. Renal insufficiency and anemia are important in recovery and postoperative mortality. Anemia leads to slower wound healing, with an increased possibility of infection. An Hb level < 11 mg/dL is associated with poor prognosis and higher mortality. In this study, Hb < 11 mg/dL (Fig. 4) and Cr > 1.2 g/dL (Fig. 3) were independent predictors of mortality, which is consistent with the literature.
Visceral metastases occurred in 58% of the patients. The lung was most commonly affected, and liver and brain metastases were next. Distant metastasis is a relevant comorbidity because it leads to organ failure and frequent hospitalizations. Thus, it is associated with poor prognosis and higher mortality. However, in this cohort, there was no statistical relationship between the presence of visceral metastasis and higher mortality. There may be a bias in this result, as only patients who underwent surgery were included in our sample; we excluded patients with visceral metastases and other metastasis who did not undergo femoral surgery. Further studies are necessary to examine this.

Overall, 29 patients (70%) died after a minimum two months of follow-up. The average time between surgery and death was 8.1 months. This high mortality and early deaths reflect the typical behavior of an aggressive disease.

In conclusion, surgeons should assess these patients globally (orthopedic and clinical factors) before a surgical procedure is decided upon, because in most cases, a palliative surgical treatment should be performed as soon as possible and allow rapid rehabilitation so that the patient can enjoy the last months of survival with the best possible quality of life.

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RESUMO

OBJETIVO: Determinar os fatores clínicos e ortopédicos relacionados com a mortalidade em pacientes com câncer de mama e metástases ao fêmur tratados cirurgicamente.

MÉTODO: Foi realizado um estudo retrospectivo que incluiu 41 pacientes submetidos ao tratamento cirúrgico de metástases fêmorais. Foram analisadas.
as seguintes variáveis: (i) número e a localização das metástases ósseas, (ii) metástases viscerais, (iii) presença de fratura patológica, (iv) método de fixação e (v) testes de laboratório. Esses fatores foram correlacionados com a mortalidade por meio de regressão logística multivariada Cox e curvas Kaplan-Meier.

RESULTADOS: Houve uma alta prevalência de metástases múltiplas associadas com fraturas patológicas, no momento da cirurgia. A mortalidade foi alta e precoce. Localização subtrocânterica, a presença de fraturas, anemia e alterações na função renal foram associados a maior mortalidade. O método de fixação, o número de metástases ósseas, e a presença de metástases em outros órgãos não alterou a mortalidade.

CONCLUSÕES: O câncer de mama com metástase para o fêmur é uma doença avançada, com mortalidade precoce. Fatores clínicos e ortopédicos deve ser considerado. A cirurgia é recomendada quando ocorrem lesões, independente do tipo de implante utilizado.

REFERENCES