ORIGINAL RESEARCH

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.

Mouraria GG, Matte SRF, Hanasilo CH, de Carvalho MJR, Etchebehere M. Prognostic factors in patients with breast cancer metastasis in the femur treated surgically. MEDICALEXPRESS. 2014 Oct;1(5):221-226.

Received for publication on May 10 2014; **First review completed on** May 21 2014; **Accepted for publication on** June 22, 2014

E-mail: ggmouraria@hotmail.com

INTRODUCTION

Breast carcinoma is a common disease in the developed world. In the presence of metastases, the bone is affected in more than 50% of patients[1]. In the appendicular skeleton, the femur is most commonly affected[2,3].

Although metastases to the axial skeleton are more frequent, metastases to the lower limbs cause greater loss of function. Bone metastases in the lower limb, even in the absence of fractures, lead to pain, functional limitations, and reduced quality of life for patients, due to strict bed rest and its complications, such as deep vein thrombosis, pneumonia, and decubitus sores[4]. The presence of fractures leads to a further increase in morbidity and mortality in these patients[5]. In practical terms, there is no specific clinical treatment for metastatic lesions in the femur[4,6].

Prognostic factors for mortality in cancer patients in general and for bone metastases have been reported. The presence of multiple bone metastasis, visceral metastasis, low hemoglobin, presence of fractures, and prosthetic replacement therapy are associated with higher mortality in this population[7–10]. However, we are aware of no report of specific prognostic factors related to metastases derived from breast cancer that occur in the femur. Thus, the aim of this study was to determine factors related to clinical orthopedic issues and mortality in this cohort of patients.

SUBJECT AND METHODS

We conducted a retrospective cohort study involving 41 women diagnosed with breast cancer metastasis in the femur who underwent surgery between 1994 and 2007. We analyzed the following orthopedic variables: (i) the number of bone metastases, (ii) the presence of pathological fractures, (iii) the fixation method used in the treatment of the metastasis (synthesis or prostheses/endoprostheses), and (iv) the topography of the metastasis in the femur. The number and location of bone metastases was determined by scintigraphy and RX. In order to establish the topography of

DOI: 10.5935/MedicalExpress.2014.05.02

the lesions, in the femur was divided into proximal (transtrochanteric 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.

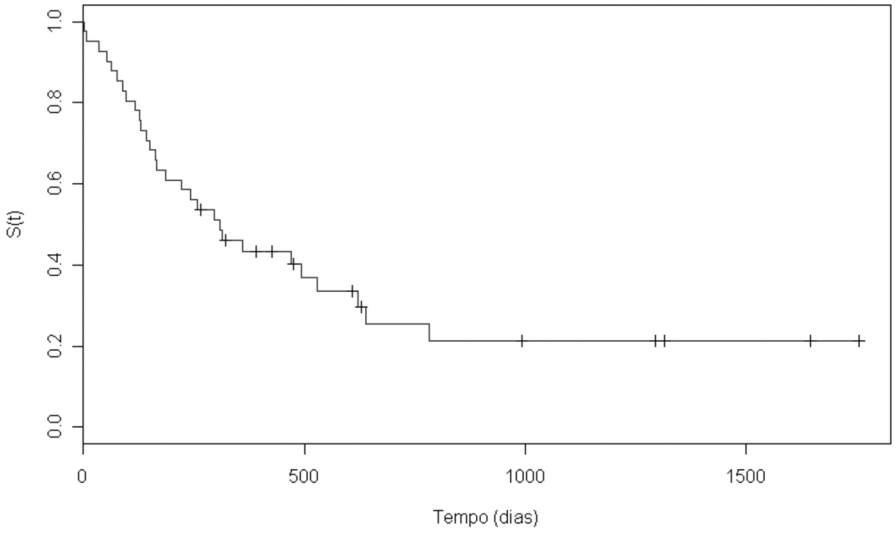


Figure 1 - Kaplan-Meyer curve for overall mortality. The median survival was 8.1 months, with 70% of deaths occurring during the first year after surgery.

Table 1 - Mortality estimates obtained by Cox multivariate logistic regression

	Variables	regression coefficient	hazard ratio (HR)	95% confidence interval		p value
				lower	upper	
	proximal(1)	−1.088	2.969(2)	1.010	4.929	0.050
Topography of lesions	diaphysis	−1.20	3.322(2)	1.362	5.820	0.050
	distal	−0.443	1.557(2)	−0.462	3.517	0.610
Hemoglobin		−0.233	1.263(3)	0.697	3.223	0.002
Urea		0.026	1.026	0.934	1.968	0.090
Creatinine		1.295	3.650(4)	1.690	5.610	0.002
Presence of fracture		1.14	3.130	1.170	5.060	0.016
Prosthetic replacement/osteosynthesis		−0.251	0.900	−1.006	2.806	0.996
Metastasis in other organs		0.419	0.400	−1.560	2.306	1.520
Number of bone metastasis		0.030	0.910	−1.010	2.900	0.987

(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.

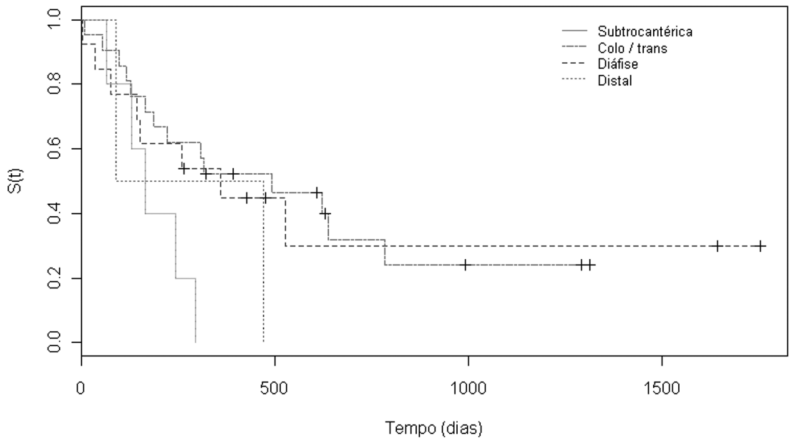


Figure 2 - The Kaplan Meyer curves for distribution of mortality according to the location of the femoral lesion. Subtrochanteric lesions are significantly worse than all other femoral locations.

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 literature[1].

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 literature[9]. 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 reports[11]. The proximal location of the lesion results in a higher probability of fracture due to

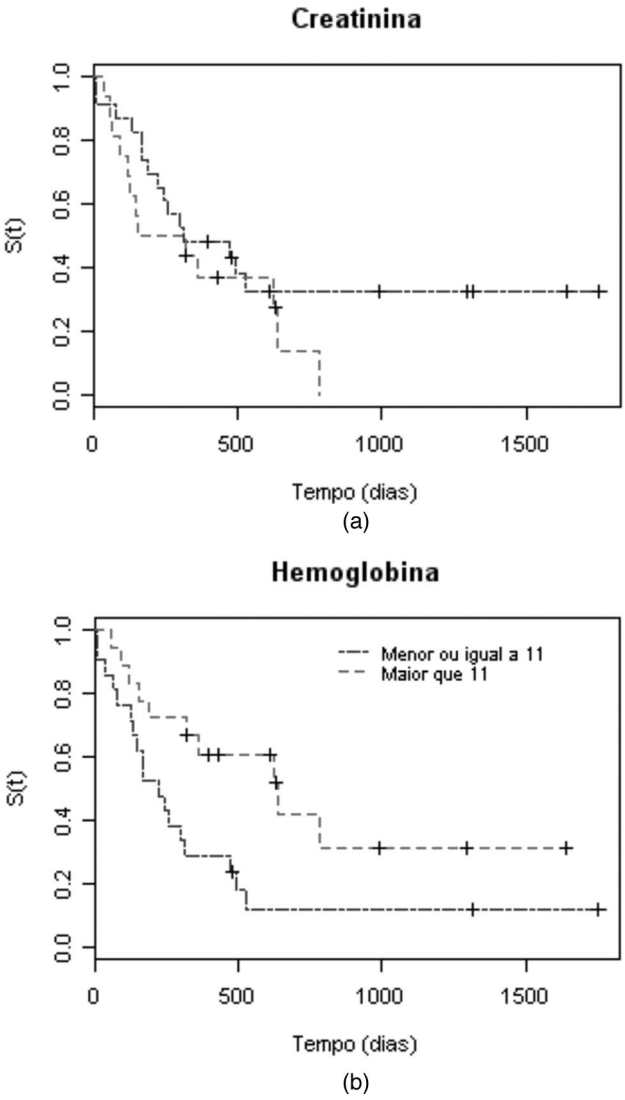


Figure 3 - Kaplan Meyer for distribution of mortality according to blood levels of creatinine (A) and hemoglobin (B). High levels of creatinine and low levels of hemoglobin significantly worsen prognosis.

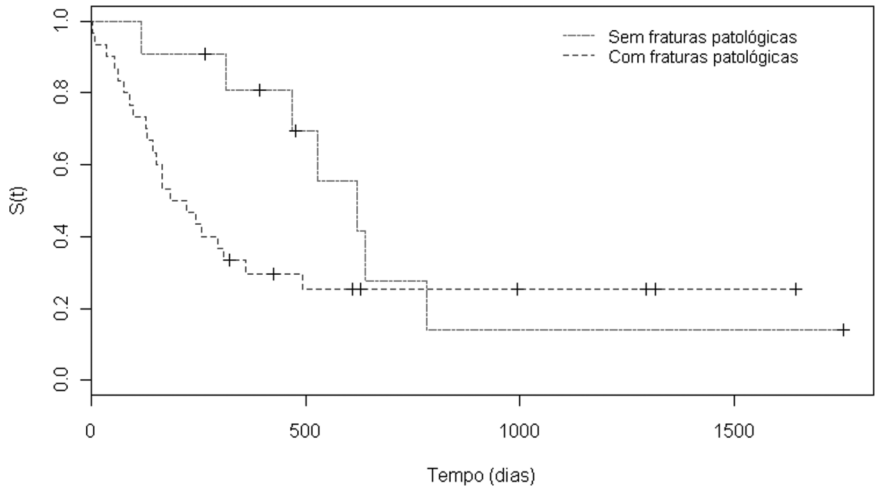
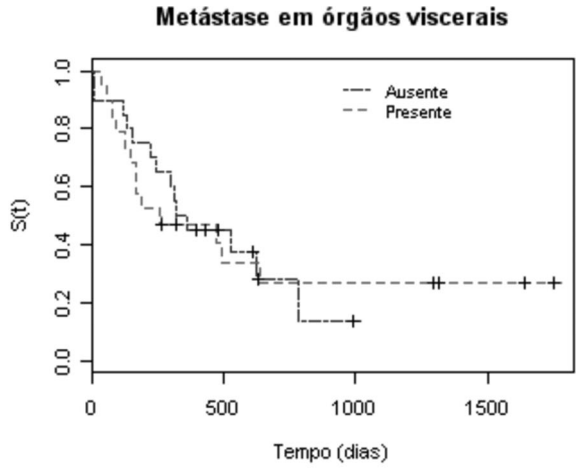
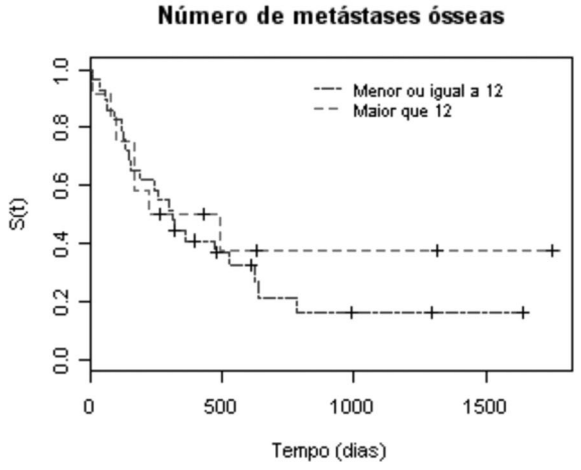


Figure 4 - Kaplan Meyer distribution of mortality according to the presence or absence of femoral fractures. The presence of fractures significantly affects mortality during the first year after surgery, but not after that.



(a)



(b)

Figure 5 - Kaplan Meyer distribution of mortality according to the presence metastases in other organs (A), or according to the number of bone metastases (B). Both significantly enhance early mortality.

mechanical forces acting on the hip[3]. Additionally, a proximal lesion more often needs prosthetic replacement, reflecting an increase in the duration of the surgery and its complications, thereby increasing mortality[12]. However, in this study, the subtrochanteric region resulted in worse prognosis, in contrast to reported data[13]. 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[14,15] 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[8].

Fractures were associated with high mortality in the first 12 postoperative months (Fig. 5), in agreement with the literature [2] 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[5]. Fractures associated with bone metastasis of breast cancer have higher mortality than do other cancers, such as those of the lung or kidney[9,15].

Clinically, renal function parameters and hemoglobin levels were, on average, normal. Renal insufficiency and anemia are important in recovery and postoperative mortality[2,17]. 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[17]. 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[17].

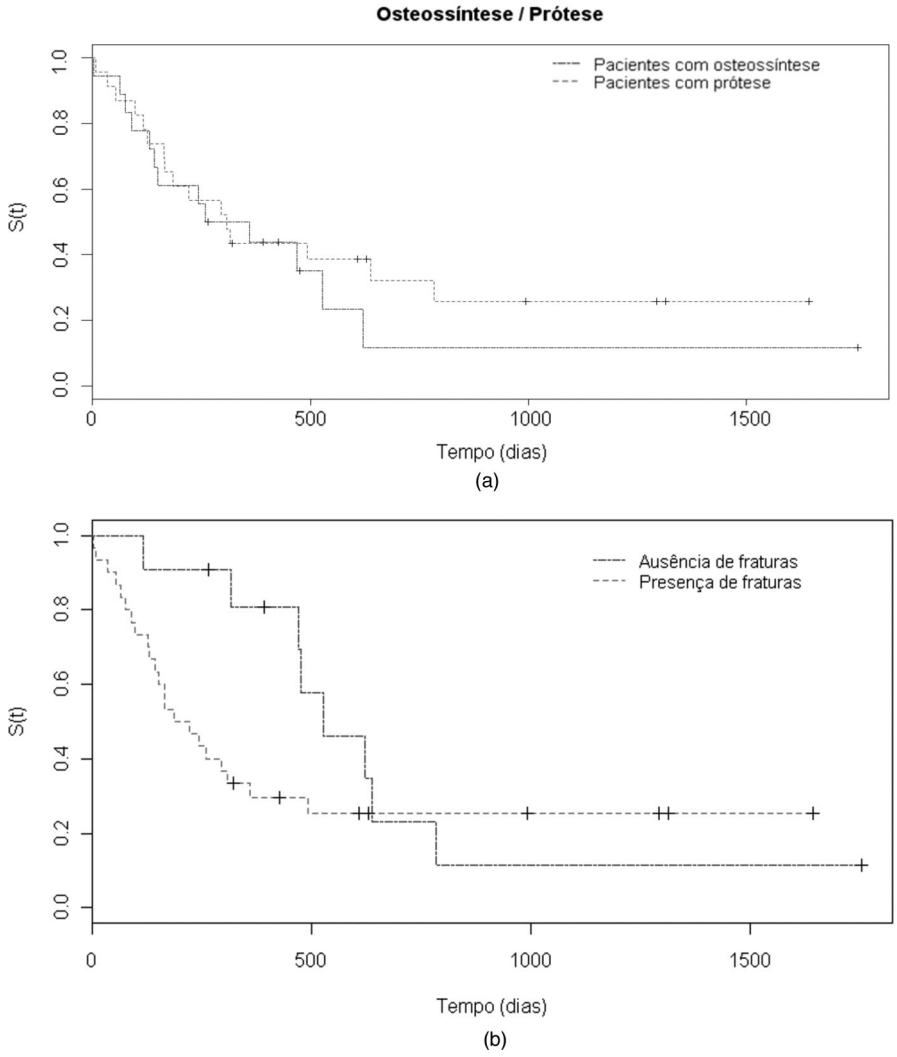


Figure 6 - Kaplan Meyer distribution of mortality according to the surgical procedure. Survival is not affected by the selection of procedure.

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[2,12]. 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 reflects 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 considered. The surgical treatment of metastasis in the femur 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.

■ ACKNOWLEDGEMENTS

The authors declare that they have no conflict of interest. There was no external funding source for this study.

■ RESUMO

INTRODUÇÃO: O carcinoma de mama é um tumor maligno comum no mundo desenvolvido. O diagnóstico tardio da doença está associada com metástases ósseas. O fêmur é comumente afetado. Fatores prognósticos de mortalidade em pacientes com metástases ósseas provenientes de cânceres em geral têm sido relatados. No entanto, não há nenhum relatório específico de fatores prognósticos em relação à metástase do câncer de mama no fêmur tratados cirurgicamente. A determinação de fatores prognósticos em pacientes com metástases ósseas pode auxiliar a tomada de decisões terapêuticas.

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 femorais. 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 subtrocantéricas, 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. Factores clínicos e ortopédicas deve ser considerado. A cirurgia é recomendada quando ocorrem lesões, independente do tipo de implante utilizado.

REFERENCES

1. Jensen AØ, Jacobsen JB, Nørgaard M, Yong M, Fryzek JP, Sørensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: A population-based cohort study in Denmark. BMC Cancer. 2011;11(Jan 24):29.
2. Narazaki DK, Alvarenga Neto CC, Caiero MT, Camargo OP. Prognostic factors in pathologic fractures secondary to metastatic tumors. Clinics. 2006;61(4):313-20.
3. Keene JS, Sellinger DS, Mcbeath AA, Engber WD. Metastatic breast cancer in femur. A search for the lesion at risk of fracture. Clin Orthop Relat Res. 1986;203:282-8.
4. Dutka J, Sosin P. Time of survival and quality of life of the patients operatively treated due to pathological fractures due to bone metastase. Ortop Traumatol Rehabil. 2003;5(3):276-83.
5. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer. 2007;110(8):1860-7.
6. Jacofsky DJ, Haidukewych GJ. Management of pathologic fractures of the proximal femur: state of the art. J Orthop Trauma. 2004;18(7):459-69.
7. Ward WG, Holsenbeck S, Dorey FJ, Spang J, Howe D. Metastatic disease of the femur: surgical treatment. Clin Orthop Relat Res. 2003; (415 Suppl): S230-44.
8. Wedin R, Bauer HCF. Surgical treatment of skeletal metastatic lesions of the proximal femur. J Bone Joint Surg Br. 2005;87(12):1653-7.
9. Katagiri H, Takahashi M, Wakai K, Sugiura H, Kataoka T, Nakanishi K. Prognostic factors and a scoring system for patients with skeletal metastasis. J Bone Joint Surg Br. 2005;87(5):698-703.
10. Laitinen M, Hansen HB, Bergh P. Long term survival in patients operated for pathological fractures in the pelvis and stremitis. 14º International Symposium of Limb Salvage. Hamburg. Proceedings. 2007.
11. Mrozek T, Spindel J, Miszczyk L, Koczy B, Chrobok A, Pilecki B, Horzela Jarosz A. The own experience in femoral bone metastases treatment. Ortop Traumatol Rehabil. 2003;5(3):335-8.
12. Bielecki T, Gazdzik TS, Jurkiewicz A. Possibilities of surgical treatment of bone metastases to the proximal epiphysis of the femur: a reviem of the literature and own experience. Ortop Traumatol Rehabil. 2003;5(3):305-12.
13. Jacofsky DJ, Haidukewych GJ. Management of pathologic fractures of the proximal femur: state of art. J Orthop Trauma. 2004;18(7):459-69.
14. Moholkar K, Mohan R, Grigoris P. The long Gamma Nail stabilization of existing and impending pathological fractures of the femur: an analysis of 48 cases. Acta Orthop Belg. 2004;70(5):429-34.
15. Weber KL, O'Connor MI. Operative of long bone metástase: focus on the femur. Clin Orthop Relat Res. 2003; (415 Suppl):S276-8.
16. Chrobok A1, Spindel J, Mrozek T, Miszczyk L, Koczy B, Tomasik P, et al. Partial long stem resection Austin – Moore Hip endoprotesis in the treatment of metastases to the proximal femur. Ortop Traumatol Rehabil. 2005;7(6):600-3.
17. Hortobagyi GN, Smith TL, Legha SS, Swenerton KD, Gehan EA, Yap HY, et al. Multivariate analysis of prognostic factors in metastatic breast cancer. J Clin Oncol. 1983;1(12):776-86.