doi: 10.4181/RNC.2014.22.02.923.6p

Survival of women with spinal compression syndrome due to bone metastasis secondary to breast cancer

Sobrevida de mulheres com síndrome de compressão medular após metástase óssea secundária ao câncer de mama

Anke Bergmann[1], Erica Nogueira Fabro[2], Blenda do Amaral e Silva[3], Ana Carolina Padula Ribeiro[4], Marianna Lou[5], Juliana Flavia de Oliveira[6], Elisangela Pedrosa[7], Luiz Claudio Santos Thuler[8]

RESUMO

Objetivo. Descrever as características, os fatores prognósticos e a sobrevida global de pacientes com síndrome de compressão após metástase óssea secundária ao câncer de mama. **Método**: Foi realizado um estudo de sobrevida em mulheres com câncer de mama e metástase óssea , com diagnóstico de síndrome de compressão medular ou radicular em uma única instituição. As características demográficas (idade, estado civil e escolaridade) e clínicas (estadiamento clínico, tratamento cirúrgico do câncer de mama, sítio da metástase, tipo de compressão e óbito) foram coletadas retrospectivamente dos prontuários médicos. Foi considerado desfecho a ocorrência de óbito e censura, os casos vivos no último seguimento. Foi realizada a Regressão de Cox com nível de significância de 95%. **Resultados**: Foram incluídos 36 casos. O tempo mediano entre o diagnóstico de câncer de mama e a metástase óssea foi de 17 meses (0-167). O óbito ocorreu em 92% dos casos, com mediana de 22 meses (1-99) após o diagnóstico de metástase óssea e 9 meses (0-47) após o diagnóstico de síndrome de compressão. A única variável associada a com o aumento da sobrevida após compressão medular foi o uso de bifosfonatos após a metástase óssea. **Conclusão**: A sobrevida global após metástase óssea foi de 22 meses e após a sindrome de compressão de 9 meses. O uso de bifosfonatos aumentou a sobrevida global após a síndrome de compressão medular.

Unitermos. Neoplasias da Mama, Síndromes de Compressão Nervosa, Taxa de Sobrevida, Metástase Neoplásica

Citação. Bergmann A, Fabro EN, Silva BA, Ribeiro ACP, Lou M, Oliveira JF, Pedrosa E, Thuler LCS. Sobrevida de mulheres com síndrome de compressão medular após metástase óssea secundária ao câncer de mama.

Trabalho realizado no Hospital do Câncer III / Instituto Nacional de Câncer, Rio de Janeiro-RJ, Brasil.

1. Fisioterapeuta, Doutora, Professora do Programa de Pós-Graduação Stricto Sensu em Ciências da Reabilitação do Centro Universitário Augusto Motta, Tecnologista do Instituto Nacional de Câncer; Rio de Janeiro-RJ, Brasil.
2. Fisioterapeuta, Mestre, Tecnologista do Instituto Nacional de Câncer; Rio de Janeiro-RJ, Brasil.
3. Fisioterapeuta, Centro Universitário Augusto Motta; Rio de Janeiro-RJ, Brasil.
4. Fisioterapeuta, Mestre; Rio de Janeiro-RJ, Brasil.
5. Fisioterapeuta, Mestre, Tecnologista do Instituto Nacional de Câncer; Rio de Janeiro-RJ, Brasil.
6. Fisioterapeuta, Doutora, Professora do Programa de Pós-Graduação Stricto Sensu em Ciências da Reabilitação do Centro Universitário Augusto Motta, Tecnologista do Instituto Nacional de Câncer; Rio de Janeiro-RJ, Brasil.
7. Fisioterapeuta, Instituto Nacional de Câncer; Rio de Janeiro-RJ, Brasil.
8. Médico, Doutor, Professor do Programa de Pós-Graduação Stricto Sensu em Neurociências da Universidade Federal do Estado do Rio de Janeiro, Tecnologista do Instituto Nacional de Câncer; Rio de Janeiro-RJ, Brasil.

ABSTRACT

Objective: describe the characteristics, associated prognostic factors and overall survival of patients with spinal compression syndrome after bone metastasis in breast cancer patients. **Method**: A survival study was performed in women with breast cancer and bone metastasis, with diagnosis of radicular and/or spinal compression syndrome at a single institution. We retrospectively collect the variables related to demographic characteristics (age, marital status and education) and clinical information (clinical stage, surgical treatment of breast cancer, site of metastasis, type of compression syndrome and death). Outcome was considered the occurrence of death and censures, the cases alive at the last follow-up. Cox regression was used on a statistically significant level of 95%. **Results**: Thirty-six cases were included. Median time between breast cancer diagnosis and bone metastasis was 17 months (0–167), and median time to compression syndrome was 30 months (0–167). Death occurred in 92% of cases, a median of 22 months (1–99) after bone metastasis diagnosis and 9 months (0–47) after diagnosis of compression syndrome. The only variable that was associated with increased survival after compression syndrome was the use of bisphosphonates after bone metastasis. **Conclusion**: Overall survival was 22 months after diagnosis of bone metastasis and 9 months after compression syndrome. Patients that had used bisphosphonates had increased survival after compression syndrome.

Keywords. Breast Neoplasms, Nerve Compression Syndromes, Survival Rate, Neoplasm Metastasis

Citation. Bergmann A, Fabro EN, Silva BA, Ribeiro ACP, Lou M, Oliveira JF, Pedrosa E, Thuler LCS. Survival of Women with Spinal Compression Syndrome Due to Bone Metastasis Secondary to Breast Cancer.

Endereço para correspondência:
Anke Bergmann
Rua André Cavalcanti, 37, 2o andar - Centro.
CEP: 20231-050, Rio de Janeiro-RJ, Brasil.
Telefone: 55 21 3207-6551
e-mail: abergmann@inca.gov.br

Original
Recebido em: 11/11/13
Aceito em: 18/05/14
Conflito de interesses: não

INTRODUCTION

The World Health Organization has estimated that there are more than 1.29 million new cases of breast cancer each year, making it the most common cancer among women. In Brazil, there were approximately 576,580 new cases of cancer in 2014, and of these, 57,120 were breast cancer[1]. Although the trend in breast cancer mortality rates has remained declined in some developed countries, in Brazil, mortality rates still increasing in some states, probably because of socioeconomic inequalities[2].

Therefore, as a result of therapeutic advances in breast cancer, patients are surviving longer, leading to an increased risk of bone metastasis and skeletal-related events[3]. It is estimated that over 50% of breast cancer patients will develop bone metastases during the course of the disease. Studies on cadavers found that 70% of patients died with evidence of this type of metastasis[4-8], and patients who experience disease progression primarily to the bone have a median survival of 24 months[6].

In breast cancer bone metastasis, the most common event (80–90%) that causes bone destruction is an osteolytic lesion, and the least frequent (10%–20%) is abormal osteoblastic bone formation. These lesions can lead to severe pain, pathological fractures, radicular and/or spinal cord compression syndrome, and hypercalcemia[3,6,8-10]. Spinal cord compression occurs in about 10% of breast cancer patients and results in serious complications that contribute directly to reducing the survival of these patients and affect their quality of life[6,11,12].

Knowledge of the characteristics of women who develop compression syndrome and the factors associated with clinical progression and survival may contribute to the development of preventative strategies and improved quality of life. To date, no studies have identified this feature in the Brazilian population.

This study aims to describe the characteristics, prognostic factors and overall survival of patients with radicular and/or spinal cord compression syndrome after bone metastasis in breast cancer patients. To meet these goals, we retrospectively collect the variables related to demographic characteristics (age, marital status and education) and clinical information (clinical stage, surgical treatment of breast cancer, site of metastasis, type of compression syndrome and death).

METHOD

Design and patients

A survival study was performed in women with breast cancer and bone metastasis, with diagnosis of radicular and/or spinal compression syndrome at a single institution, between May 2006 and April 2007. We excluded those undergoing cancer treatments outside the institution prior to enrollment and patients with an epidural mass. The patients were followed up until April 2010. The study was approved by the institution's research and ethics committee (CEP INCA Nº016/08).

Procedure

The physiotherapy routine of the institution recommends the evaluation of all patients admitted for clinical treatment and referred by the health team for outpatient care using a validated instrument[13]. Thus, it was possible to retrospectively collect the variables related to demographic characteristics (age, marital status and education) and clinical information (clinical stage, surgical treatment of breast cancer, site of metastasis, type of compression syndrome and death). Outcome was considered the occurrence of death and censures, the cases alive at the last follow-up.

Statistical analysis

To describe the profile of patients with compression syndrome, we performed a descriptive analysis of central and dispersion tendencies for continuous variables and absolute and relative frequencies for dichotomous variables. The Kaplan-Meier method was used to evaluate overall survival, based on a statistically significant confidence interval of 95% and p-value of <0.05. Cox regression (enter method) was used to adjust the effect of clinical stage and age at breast cancer diagnosis in relation to clinical and demographic variables and overall survival. The final model was based on a statistically significant level of 95%.

Post-hoc power analysis was conducted to determine whether sufficient power existed to observe an effect, assuming the effect size in the sample is equal to the effect size in the population (Type II error). The power statistical test was performed, considering the follow-up time required to enroll all patients (accrual time), a

significance level of 95%, the follow-up interval, the total number of patients included and the hazard ratio of the predictive variable.

RESULTS

During the study period, 36 women were found to have compression syndrome. The mean age at diagnosis of breast cancer was 53±13.8 years; 36% of them lived with a partner, and 67% had a low educational level (up to 8 years of study). Breast cancer was diagnosed at clinical stage III in 52% and stage IV in 19% of cases. Surgical treatment was possible in 58% of the patients. Metastasis in the liver (28%), lung (14%) and central nervous system (8.3%) was observed concomitant with the bone implant.

The median time between admission to hospital (to start breast cancer treatment) and bone metastasis was 17 months (0–167), and the median time until compression syndrome was 30 months (0–167). Following the diagnosis of bone metastasis, the median time until compression syndrome was 1 month (0–92).

Before the diagnosis of compression syndrome, there was at least one report of back pain in the medical records in 47% of cases. At the time of diagnosis, there were reports of back pain in the lower limbs in 24% and 29%.

Spinal cord compression syndrome occurred in 58% of the cases, radicular syndrome in 36%, and both (spinal cord and radicular) in 6%. Spinal cord compression occurred more frequently in the dorsal region (72%) and radicular compression in the second (29%) and fifth lumbar vertebra (29%; Table 1).

Palliative treatment for compression syndrome after bone metastasis was performed in all patients. The treatment used was chemotherapy in 61.1%, bisphosphonates in 75%, radiotherapy in 100% and hormone therapy in 69.4%. All patients underwent physical therapy, and in 97%, orthesis was adapted to stabilize the spine.

Death occurred in 91.7% of cases. The median overall survival was 45 months after admission (95% CI 25–66), 22 months after bone metastasis (95% CI 20–34), and 9 months after compression syndrome (95% CI 3–14; Figure 1).

Table 1
Characteristics of compression syndrome (n = 36)

Variable	n	Percentage (%)
Compression Syndrome		
Spinal cord	21	58.3
Radicular	13	36.1
Spinal cord and radicular	02	5.6
Site of the Compression Syndrome		
Dorsal	18	72.0
Cervical	04	16.0
Lumbar	03	12.0
Site of Radicular Compression		
2nd lumbar vertebra	05	29.4
3rd lumbar vertebra	03	17.6
4th lumbar vertebra	04	23.5
5th lumbar vertebra	05	29.4

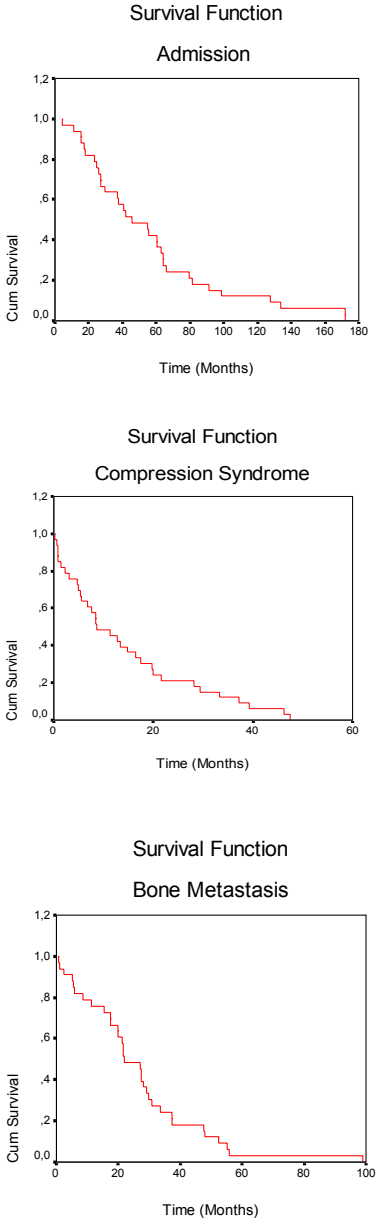

Figure 1.
Overall survival after first breast cancer treatment, radicular and/or spinal cord injury and bone metastasis

Women with single bone metastasis presented better survival (mean of 22 months) than those with bone and other sites of metastasis (mean 12 months) (p<0.043). Those patients that used bisphosphonates after bone metastasis had a mean of 22 months survival and those without this therapy had 12 months (p<0.043; Table 2).

In patients who underwent breast cancer surgery (n=21), the number of lymph nodes removed was associated with worst survival (p<0.020; Table 3).

After adjusting for the effect of age and clinical stage, the only variable that was associated with increased survival after compression syndrome was the use of bisphosphonates after bone metastasis (HR=9.28; IC 95% 2.82–30.62; p<0.001).

The post-hoc power analysis demonstrated that with a total of 36 patients included in this study, there was a 98% probability that the study would detect a difference at a significance level of 5%, with a true hazard ratio of 9.00. This was based on the assumption that the accrual period was 36 months, with a follow-up period of 36 months.

DISCUSSION

Breast cancer is an important public health problem[2]. Cancer treatment and other aging-related disease can lead to the development of skeletal events. In young women, the chemotherapy can cause early menopause and decreased bone mineral density. The estrogen-inhibiting can affect bone tissue metabolism. These conditions can adversely affect the quality of life of these patients[14]. Bone metastasis occurs very frequently in breast cancer patients. Patients with bone metastasis have a high risk of developing skeletal-related events such as vertebral compression syndrome, which can affect the quality of life and overall survival[7]. The incidence of bone metastasis after breast cancer were observed in more than 3% of patients with stages III and IV[4]. The risk factors include node status, histological classification of the tumor, nuclear grading of the tumor, size, estrogen and progesterone receptor status, and clinical stage, among other parameters. In this study, our goal was not to evaluate the risk factors for bone metastasis after breast cancer treatment, but to assess the factors associated with overall survival

Table 2
Clinical and demographic characteristics of compression syndrome (n=36).

		Survival Time (months)		
Variable	**n***	Mean	(95% CI)	**p**
Age at breast cancer diagnosis				
<50 years	16	17.58	10.24-24.92	0.989
≥50 years	20	16.17	9.08-23.26	
Years of schooling				
<8 years	20	17.43	11.48-23.38	0.684
≥8 years	10	18.45	5.76-31.14	
Marital status at breast cancer diagnosis				
Lives with partner	12	15.06	7.38-22.74	0.352
Lives without partner	21	19.77	12.79-26.76	
Oestrogen receptor				
Positive	23	17.47	11.29-23.66	0.071
Negative	08	8.53	2.58-14.49	
Progesterone receptor				
Positive	12	13.77	5.19-22.34	0.843
Negative	19	15.74	9.81-21.68	
Histological grade (Elston)				
1	0	--	--	0.965
2	13	16.34	7.65-25.02	
3	05	16.13	0.0-33.58	
Histological type				
Infiltrating ductal carcinoma	30	16.65	11.33-21.96	0.179
Others	02	5.06	0.00 -11.99	
Clinical stage (TNM)				
III and IV	25	15.15	9.36-20.93	0.311
I and II	11	20.87	10.63-31.11	
Metastasis				
Bone	16	22.26	13.60-30.94	0.043
Bone and other sites	20	12.37	7.16-17.58	
Type of compression syndrome				
Spinal cord	21	14.02	8.26-19.77	0.255
Radicular	13	21.71	12.19-31.22	
Spinal cord + radicular	02	9.93	7.12-12.79	
Use of bisphosphonates after bone metastasis				
No	09	4.34	0.30-8.38	0.001
Yes	27	20.91	15.11-26.71	
Palliative chemotherapy				
No	14	13.52	5.65-21.39	0.448
Yes	21	18.60	12.27-24.93	
Palliative hormoniotherapy				
No	12	11.17	4.42-17.93	0.085
Yes	21	19.39	12.84-25.93	

* Discrepancies in the total values correspond to missing values in each variable.

in women with compression syndrome after bone metastasis.

This study included 36 patients with compression syndrome after bone metastasis, comprising all cases of compression syndrome occurring in a single reference institution for breast cancer treatment, between May 2006 and April 2007. The average age at diagnosis of breast cancer was 53 years, and most were diagnosed at the advanced clinical stage (52% stage III and 19% stage IV). In a population-based cohort study, was reported a median age of 67 years among those who developed bone metastasis and skeletal-related events, with the highest incidence observed among patients with advanced stage tumours[7].

The median time until compression syndrome after bone metastasis was 1 month (0–92). The largest increase in skeletal-related events after bone metastasis occurs in the first year (1-year cumulative incidence = 38.5%)[7]. Our data probably indicate a late diagnosis of bone metastases in our institution.

Spinal cord compression occurred most frequently (72%) in the dorsal region in this study. Bone metastasis predominantly causes osteolytic lesions characterized by increased bone degradation that can result in pain[7]. We found that 47% of our patients had reported back pain in the medical records before the diagnosis of compression syndrome, and at the time of diagnosis, there were reports of back pain in the lower limbs in 24% and 29%.

In this study, death occurred in 92% of cases, 9 months (95% CI 3–14) after the diagnosis of compression syndrome. A similar result was found in others studies, who reports that the overall survival of patients with compression syndrome was 9 months[15] and 12 months[16] after the development of neurological signs. Significantly, longer survival is associated with a longer interval between diagnosis of the tumor and the development of compression syndrome[12].

The most frequent treatment for metastatic spinal cord compression is radiotherapy alone, although some studies have suggested that selected patients benefit more from surgery plus radiotherapy[17-19]. The indication for surgical treatment depends of the clinical status of the patients, prognosis, primary tumor and the characteristics of the spinal compression[20]. In our institution, surgery is not routine treatment for patients with compression syndrome, thus, all patients received radiotherapy, and there was no woman underwent surgery. This may also reflect the unfavorable conditions of our population.

Table 3
Clinical and demographic characteristics of compression syndrome (n=36).

		Survival Time (months)		
Variable	**n***	Mean	(95% CI)	**p**
Breast surgery				
Mastectomy	18	17.20	8.81-25.59	0.988
Conservative breast surgery	03	18.77	4.92-32.62	
Pathological lymph node status				
Negative	18	18.64	11.70-25.57	0.505
Positive	17	14.44	7.23-21.65	
Number of lymph nodes removed				
<14 lymph nodes	06	32.77	17.70-47.85	0.020
≥15 lymph nodes	14	11.55	4.06-18.65	
Number of positive lymph nodes				
0 lymph nodes	05	21.10	8.01-34.19	0.244
1–3 lymph nodes	07	19.81	7.80-31.81	
≥4 lymph nodes	08	10.82	0.00-21.67	

* Discrepancies in the total values correspond to missing values in each variable

The bisphosphonates are important bone desorption inhibitors that diminish the recruitment and activity of osteoclasts and increase their apoptosis[14]. These effects make bisphosphonates a treatment choice in many bone diseases characterized by an increase in osteoclastic desorption, such as Paget's disease, fibrous dysplasia, osteogenesis imperfect, reflex sympathetic dystrophy syndrome, vertebral fracture and osteoporosis[21,22]. In breast cancer patients, the use of bisphosphonates aim to prevent and/or treat cancer-related bone complications[3,4,6]. In our study it was not possible to obtain information of the bone characteristics prior to bone metastasis or compression syndrome. After adjustment for age and clinical stage, we found that the only variable that was associated with increased survival after compression syndrome was the use of bisphosphonates after bone metastasis.

This study aimed to describe the characteristics and survival of a series of women with vertebral com-

pression syndrome after bone metastasis in a single institution. We included all cases diagnosed between May 2006 and April 2007 at a single institution in Brazil. Due to the small number of patients enrolled, this study may have limited power to detect a significant difference (Type II error) between the survival rate and the clinical and histopathological variables. However, the use of bisphosphonates for bone metastasis was an important predictor of improved survival, with a power to detect this association of 98%.

Given the lack of information about the subject in the literature, this exploratory study may be useful in clinical practice and in designing future studies with a larger sample of patients.

CONCLUSION

In this study, women were young when diagnosed with clinically advanced breast cancer. The median time between registration in the institution for treatment of breast cancer and bone metastasis was 17 months and the median time to compression syndrome was 30 months. Overall survival was 22 months after the diagnosis of bone metastasis and 9 months after spinal cord or radicular compression syndrome. After adjustment for age and clinical stage, the only variable that was associated with increased survival after compression syndrome was the use of bisphosphonates after bone metastasis.

Studies with larger sample sizes and that, in addition to clinical and demographic characteristics, include molecular variables, must be performed to identify predictors of overall survival after bone metastasis and compression syndrome.

http://dx.doi.org/10.1590/S1807-59322011000400010 6-0

REFERENCES

1.Estimativa 2014: Incidência de Câncer no Brasil (endereço na Internet). Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva. (última atualização 12/2013; citado em 05/2014). Disponível em: http://www.inca.gov.br/estimativa/2014/sintese-de-resultados-comentarios.

2.Freitas-Junior R, Gonzaga CMR, Freitas NMA, Martins E, Dardes RCM. Disparities in female breast cancer mortality rates in Brazil between 1980 and 2009. Clinics 2012;67:731-7. http://dx.doi.org/10.6061/clinics/2012(07)05

3.Polascik TJ. Bisphosphonates in oncology: evidence for the prevention of skeletal events in patients with bone metastases. Drug Des Devel Ther 2009; 21:27-40.

4.Koizumi M, Yoshimoto M, Kasumi F, Iwase T. An open cohort study of bone metastasis incidence following surgery in breast cancer patients. BMC Cancer 2010;21:381. http://dx.doi.org/10.1186/1471-2407-10-381

5.Galasko CS. Bone metastases studied in experimental animals. Clin Orthop Relat Res 1981;155:269-85.

6.Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12(20 Pt 2):6243s-9. http://dx.doi.org/10.1053/ctrv.2000.0210

7.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;24:29. http://dx.doi.org/10.1186/1471-2407-11-29

8.Akhtari M, Mansuri J, Newman KA, Guise TM, Seth P. Biology of breast cancerbone metastasis. Cancer Biol Ther 2008;7:3-9.

9.Barlev A, Song X, Ivanov B, Setty V, Chung K. Payer costs for inpatient treatment of pathologic fracture, surgery to bone, and spinal cord compression among patients with multiple myeloma or bone metastasis secondary to prostate or breast cancer. J Manag Care Pharm 2010;16:693-702.

10.Clezardin P, Teti A. Bone metastasis: pathogenesis and therapeutic implications. Clin Exp Metastasis 2007;24:599-608. http://dx.doi.org/10.1007/s10585-007-9112-8

11.Vrionis FD, Small J. Surgical management of metastatic spinal neoplasms. Neurosurg Focus 2003;15:E12.

12.Agarawal JP, Swangsilpa T, Van Der Linden Y, Rades D, Jeremic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. Clin Oncol 2006;18:747-60. http://dx.doi.org/10.1016/j.clon.2006.09.007

13.Bergmann A, Ribeiro MJP, Pedrosa E, Nogueira EA, Oliveira ACG. Fisioterapia em mastologia oncológica: rotinas do Hospital do Câncer III / INCA. Rev Bras Cancerol 2006;52:97-109.

14.Fontanges E, Fontana A, Delmas P. Osteoporosis and breast cancer. Joint Bone Spine 2004;71:102-10. http://dx.doi.org/10.1016/j.jbspin.2003.02.001

15.Eriks IE, Angenot EL, Lankhorst GJ. Epidural metastatic spinal cord compression: functional outcome and survival after inpatient rehabilitation. Spinal Cord 2004;42:235-9. http://dx.doi.org/10.1038/sj.sc.3101555

16.Bartels RH, Feuth T, Rades D, Hedlund R, Villas C, van der Linden Y, et al. External validation of a model to predict the survival of patients presenting with a spinal epidural metastasis. Cancer Metastasis Rev 2011;30:153-9. http://dx.doi.org/10.1007/s10555-011-9271-6

17.Patchell RA. New developments in the surgical management of spinal cord compression caused by metastatic tumor. Clin Neurosurg 2005;52:65-7.

18.Tancioni F, Navarria P, Mancosu P, Pedrazzoli P, Morenghi E, Santoro A, et al. Surgery Followed by Radiotherapy for the Treatment of Metastatic Epidural Spinal Cord Compression From Breast Cancer. Spine 2011;36:E1352-9. http://dx.doi.org/10.1056/NEJM199002223220802

19.López-O R, Vicente J, Orient-López F, Fontg-Manzano F, Fernández-Mariscal E, Combalía A, et al. Pathological Vertebral Compression Fracture of C3 Due to a Breast Cancer Metastasis in a Male Patient. Spine 2009;34:E586-90. http://dx.doi.org/10.1097/BRS.0b013e3181aa2687

20.Teixeira WGJ, Coutinho PRM, Marchese LD, Narazaki DK, Cristante AF, Teixeira MJ, et al. Interobserver agreement for the spine instability neoplastic score varies according to the experience of the evaluator. Clinics 2013;68:213–7. http://dx.doi.org/10.6061/CLINICS/2013(02)OA15

21.Orcel P, Beaudreuil J. Bisphosphonates in bone diseases other than osteoporosis. Join Bone Spine 2002;69:19-27. http://dx.doi.org/10.1016/S1297-319X(01)00336-0

22.Alev C, Umay E, Polat S, Ecerkale O, Cakci A. The relationship between bisphosphonate use and demographic characteristics of male osteoporosis patients. Clinics 2011;66:579-82. http://dx.doi.org/10.1590/S1807-59322011000400010 6-0