

Prognostic Factors and Functionality in Metastatic Spinal Cord Compression: Cohort Study

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Fatores Prognósticos e Funcionalidade na Síndrome de Compressão Medular Metastática: um Estudo de Coorte
Factores Pronósticos y Funcionalidad a Síndrome de Compresión Espinal Metástasico: un Estudio de Cohorte

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ABSTRACT

Introduction: Metastatic Spinal Cord Compression (MSCC) has great potential of irreversible loss of motor and sensory function, and it is considered an oncological emergency. **Objective:** Evaluate the prognosis of MSCC and the functionality of patients with solid tumors. **Method:** Cohort study was conducted in patients with cancer who developed MSCC between January 2017 and December 2018. Clinical and socio-demographic data were extracted from physical and electronic charts. Survival analysis was performed by the Kaplan-Meier method. **Results:** The study included 90 patients who were diagnosed with MSCC. At the time of MSCC diagnosis, 55.5% of patients were unable to walk. Patients with MSCC after lung cancer had 4.1-fold more odds of death (95% CI: 1.79-9.41; $p=0.001$), those with genitourinary tumors, 1.9-fold higher risk of death (95% CI: 1.06-3.45; $p=0.02$), and with other types of tumors, 3.1-fold higher risk of death (95% CI: 1.58-6.24; $p=0.001$) when compared with patients with MSCC after breast cancer. **Conclusion:** The clinical relevance of this study relies on the findings that the primary type of tumor is a predictive factor for overall survival of MSCC. More than half of the patients were unable to walk at the MSCC diagnosis.

Key words: spinal cord compression; spinal neoplasms; neoplasm metastasis; prognosis.

RESUMO

Introdução: A síndrome de compressão medular metastática (SCMM) tem grande potencial de perda irreversível da função motora e sensitiva, sendo considerada uma emergência oncológica. **Objetivo:** Avaliar o prognóstico da SCMM e a funcionalidade dos pacientes com tumores sólidos. **Método:** Estudo de coorte que incluiu pacientes com câncer que desenvolveram SCMM entre janeiro de 2017 e dezembro de 2018. Os dados clínicos e sociodemográficos foram extraídos dos prontuários físicos e eletrônicos. Análise de sobrevida foi realizada pelo método Kaplan-Meier. **Resultados:** O estudo abrangeu 90 pacientes que apresentaram SCMM. Ao diagnóstico da SCMM, 55,5% dos pacientes não conseguiam realizar marcha. Os pacientes com SCMM após câncer de pulmão tiveram 4,1 vezes maior risco de morrer (IC 95%, 1,79-9,41; $p=0,001$), os pacientes com tumores genitourinários tiveram 1,9 vezes maior risco de morrer (IC 95%, 1,06-3,45; $p=0,02$) e os pacientes com outros tipos de tumor tiveram 3,1 vezes maior risco de morrer (IC 95%, 1,58-6,24; $p=0,001$) quando comparados aos pacientes com SCMM após câncer de mama. **Conclusão:** Destaca-se a relevância clínica deste estudo ao descobrir que o tipo de tumor primário é um fator preditor independente para sobrevida da SCMM. Ao diagnóstico da SCMM, mais da metade dos pacientes não realizam marcha.

Palavras-chave: compressão da medula espinal; neoplasias da coluna vertebral; metástase neoplásica; prognóstico.

RESUMEN

Introducción: El síndrome de compresión espinal (SCE) tiene un gran potencial de pérdida irreversible de la función motora y sensorial, siendo considerado una emergencia oncológica. **Objetivo:** Evaluar el pronóstico de SCE y la funcionalidad de los pacientes. **Método:** Estudio de cohorte que incluyó pacientes con cáncer que desarrollaron SCE entre enero de 2017 y diciembre de 2018. Se extrajeron datos clínicos y sociodemográficos de historias clínicas físicas y electrónicas. El análisis de supervivencia se realizó mediante el método de Kaplan-Meier. **Resultados:** El estudio cubrió a 90 pacientes que tenían SCE. En el diagnóstico de SCE, 55,5% de los pacientes no pueden caminar. En comparación con los pacientes con cáncer de mama, los pacientes con cáncer de pulmón tenían 4,1 veces más riesgo de morir (IC 95%, 1,79-9,41; $p=0,001$), los pacientes con tumores genitourinarios 1,9 veces mayor de morir (IC 95%, 1,06-3,45; $p=0,02$) y aquellos pacientes con otro tipo de tumor, 3,1 veces mayor riesgo de morir (IC 95%, 1,58-6,24; $p=0,001$). **Conclusión:** Este estudio encontró que el tipo de tumor primario es un factor predictivo para la supervivencia de le SCE. Más de la mitad de los pacientes no caminan en el momento del diagnóstico de SCE. **Palabras clave:** compresión de la médula espinal; neoplasias de la columna vertebral; metástasis de la neoplasia; pronósticos.

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INTRODUCTION

Recently, the incidence of non-traumatic spinal cord injuries has been increasing. The etiology of these injuries can be categorized as degenerative, infectious, vascular and neoplastic^{1,2}.

Cancer has become one of the major global public health problems³ due to population ageing. For each year of the triennium 2020-2022, 625 thousand new cases of cancer are estimated⁴.

The inclusion of new therapeutic modalities favor cancer treatment and relapses (metastasis) which increase the survival of oncologic patients; however, this does not mean they are cured, and new metastases can appear in the skeletal system. The development of bone metastases in oncologic patients can cause lytic or osteoblastic injuries⁵⁻⁷, which tend to compromise the efficacy of the skeletal system in neutralizing mechanic burden, can cause pain and pathological fractures, for instance, in vertebrae⁵⁻⁷.

Vertebral collapse and increase of formation of neoplastic bone tissue augment the risk of medullary canal invasion possibly compressing neural structures, causing the metastatic spinal cord compression syndrome (MSCC)^{8,9}. This syndrome has great potential of causing irreversible loss of motor and sensory functions and it is considered an oncological emergency requiring prompt diagnosis and management^{10,11}.

The incidence of this disorder can vary significantly according to the type of primary tumor^{12,13}. The incidence of MSCC in patients with pancreatic cancer is 0.6% and in patients with lung cancer, 4%^{11,13}.

The main neurologic manifestation at the diagnosis for 80% to 95% of the individuals is pain in the spinal column, but other manifestations are found: sensory alterations, sphincter disorder and motor weakness. Disablement of muscle strength can be detected in 35% to 75% of the patients with direct impact on their functional independence causing since gait problems up to paralysis of body structures below the level of injury and negatively impacting the quality-of-life^{9-11,14}.

Most of the times, these patients have a dismal prognosis with potential death in few months. Currently, the clinical course of MSCC in the Brazilian population is poorly elucidated. New data about the functionality of the patients and identification of survival prognostic factors are essential to understand this complication, helping to guide better therapeutic strategies and patient-centered treatment. The objective of this study was to evaluate the prognosis and functionality of patients with MSCC.

METHOD

Cohort study with patients with MSCC between January 2017 and December 2018. The study population

was identified through the “*Sistema de Controle de Atendimento do Serviço de Fisioterapia (SISCASF)*”, being eligible the cases where planning and treatment were exclusively conducted at the National Cancer Institute José Alencar Gomes da Silva (INCA). Patients with hematologic neoplasms and under 18 years of age were excluded.

MSCC was defined by radiologic and clinical criteria as compression, indentation, displacement or lining of the dural sac involving the spinal cord and cauda equina¹¹. Its diagnosis was confirmed with magnetic resonance, computed tomography or positron-emission tomography (PET).

Clinical and epidemiologic data were extracted from paper and electronic charts from the diagnosis of cancer up to death, loss-to-follow-up or end of the study. The variables investigated were sex, age, race, marital status, education, type of cancer treatment, type of primary tumor, type of treatment for MSCC, number of metastases prior to MSCC, metastatic sites, number of vertebra affected, performance status (PS), ambulation and motor function.

The main aspects of the results are presented in tables and figures highlighted in the text. Measures of central tendency and dispersion for continuous variables and distribution of frequency for the categorical were utilized for descriptive analysis of the study population. Kaplan-Meier was utilized to analyze survivorship for exploratory evaluation among independent variables and time to outcomes. Log-rank test was calculated to identify if the differences among the curves were statistically significant.

The outcomes were global survivorship and time between the diagnosis of MSCC up to death or date of end of follow-up (31/12/2019) or last visit at the hospital (censorship).

All the variables with value of $p < 0.20$ were selected for Cox multiple regression with the method Stepwise Forward, to estimate the independent factors associated with death. The values of $p \leq 0.05$ were considered statistically significant for all the analyzes. Data were processed and analyzed through software Statistical Package for Social Science (SPSS) for Windows, São Paulo, Brazil, version 21.0.

The Institutional Review Board of INCA, CAAE 89670418.0.00000.5274, report 2.714.857 approved the study on July 15, 2018.

RESULTS

In all, 90 patients with MSCC (Figure 1) were enrolled and mean age at diagnosis was 54 years (± 12.5).

Most of the patients were women (70.0%), White (34.4%), married (46.7%), low education (50.0%), with

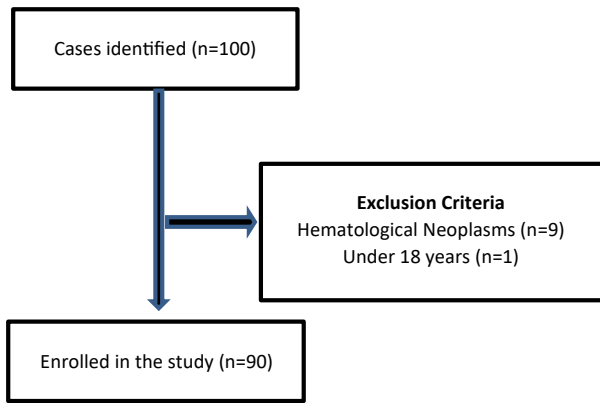


Figure 1. Eligibility

breast cancer (46.7%), followed by genitourinary tumors (27.8%), lung cancer (11.1%) and others (14.4%). Chemotherapy was the cancer treatment most utilized (82.2%) followed by surgery (41.1%), radiotherapy (32.2%) and six patients (6.6%) did not undergo specific treatments.

Median time between cancer diagnosis and development of MSCC was 20 months (CI95%, 5.59-35.54).

The most common initial symptom was pain in the spine column (81.1%). The most affected segments of the spine were thoracic (58.8%), lumbosacral (15.6%) and cervical column (10.0%). In total, 14 patients (15.6%) presented MSCC in multiple levels of the spine.

At the diagnosis of MSCC, 11 patients (12.2%) had sphincter dysfunction and 17 patients (18.9%) utilized bladder catheter for incontinence. Regarding motor function, 10 patients (11.2%) had no dysfunction, 26 (28.9%) had motor dysfunction but with gait secured, 31 patients (34.4%) presented severe motor dysfunction and were unable to perform gait and 19 patients (21.2%) had complete loss of the motor function below the level of the injury (Table 2).

In all, 85 patients (94.4%) were admitted. During hospitalization, 15 patients (17.6%) died, 70 patients (82.4%) were discharged and 42 patients (46.7%) submitted to outpatient physiotherapy. At hospital discharge, seven patients (7.8%) had no motor dysfunction, 24 patients (26.7%) had moderate motor dysfunction but were able to ambulate, 24 patients (26.7%) had severe motor dysfunction and were unable to ambulate and 12 patients (13.3%) had total loss of the motor function below the level of the injury (Table 2).

Median time of hospitalization of patients with breast cancer was 18 days, with lung cancer, nine days, genitourinary, 22 days and with other types of solid tumors, 16 days, a statistically significant difference ($p=0.01$).

Table 1. Sociodemographic characteristics of patients with MSCC (n=90)

Characteristics	n (%)
Sex	
Male	27 (30.0)
Female	63 (70.0)
Age at diagnosis of MSCC	
≤60 years	65 (72.2)
>60 years	25 (27.8)
Ethnicity	
White	31 (34.5)
Black	18 (20.0)
Brown	39 (43.3)
Indigenous	1 (1.1)
Missing	1 (1.1)
Marital Status	
Married	42 (46.7)
Separated	5 (5.6)
Widow/Widower	13 (14.4)
Single	28 (31.1)
Missing	2 (2.2)
Education	
≤8 years	45 (50.0)
>8 years	41 (45.6)
Missing	4 (4.4)
Types of cancer treatment*	
Chemotherapy	74 (82.2)
Surgery	37 (41.1)
Radiotherapy	29 (32.2)
None	6 (6.6)
Types of primary tumor	
Breast	42 (46.7)
Lung	10 (11.1)
Genitourinary	25 (27.8)
Others	13 (14.4)
Types of MSCC treatment	
Radiotherapy	72 (80.0)
Surgery	8 (8.9)
Others	10 (11.1)
Number of metastases prior to MSCC	
≤1 metastasis	46 (51.1)
>1 metastasis	44 (48.9)

to be continued

Table 1. continuation

Characteristics	n (%)
Liver Metastasis	
Yes	13 (14.4)
No	77 (85.6)
Number of vertebra affected	
≤2 vertebra	27 (30.0)
> 2 vertebra	63 (70.0)
Performance status	
≤2	65 (72.2)
>2	25 (27.8)
Missing	
Ambulation	
Yes	31 (34.5)
No	18 (20.0)
Missing	39 (43.3)
Missing	1 (1.1)

Caption: MSCC = Metastatic spinal cord compression syndrome.

(*) More than one treatment possibly simultaneous.

Table 2. Clinical characteristics of the patients with MSCC (n=90)

Characteristics	n (%)
Spinal column segments affected*	
Cervical	10 (10.0)
Thoracic	53 (58.8)
Lumbosacral	14 (15.6)
Multiple	14 (15.6)
Bladder function at MSCC diagnosis	
Normal	55 (61.1)
Bladder dysfunction	11 (12.2)
Incontinence with bladder catheter	17 (18.9)
No information	7 (7.8)
Motor function at MSCC diagnosis	
Without motor dysfunction	10 (11.2)
Motor dysfunction, gait secured	26 (28.9)
Severe motor dysfunction, gait impairment	31 (34.4)
Total loss of motor function	19 (21.1)
No information	4 (4.4)
Motor function at hospital discharge (n=70)	
Without motor dysfunction	7 (7.8)
Motor dysfunction, gait secured	24 (26.7)
Severe motor dysfunction, gait impairment	24 (26.7)
Total loss of motor function	12 (13.3)
No information	3 (3.3)

Caption: MSCC = Metastatic spinal cord compression syndrome.

(*) More than one segment might have been affected simultaneously.

72 (80.0%) patients treated MSCC with radiotherapy, eight (8.9%), underwent surgery and ten (11.1%) another type of treatment. In addition, 46 (51.1%) utilized bisphosphonate after the diagnosis. Ultimately, 52 patients (57.8%) were referred to specialized hospitals in palliative care (data not shown in the tables).

Table 3 summarizes the estimates of the survival time of patients with MSCC. In three months, 65.5% of the patients were alive, in six months, 47.5% and in 12 months, 33.6%. Median survival time of these patients was 5.2 months (CI 95%, 3.42-7.02).

Median survival time for patients with breast cancer was 12.6 months, for patients with genitourinary tumors, 4.1 months, for lung cancer, 3.1 months and for other solid tumors, 2.6 months ($p < 0.001$) as shown in Table 3 and Graph 1. For those with up to two vertebra affected, the mean survival time was 6.3 months and more than two vertebra affected, 4.1 months ($p = 0.04$). The mean survival time of the patients who ambulated was 7.9 months and for those who didn't, 3.6 months ($p = 0.01$).

After adjustments by the variables with significance of $p < 0.20$, the multivariate analysis revealed that, compared to those patients with breast cancer, patients with lung cancer had 4.1-fold more odds of death (CI 95%, 1.79-9.41; $p = 0.001$); the patients with genitourinary cancer had 1.9-fold more odds of death (CI 95%, 1.06-3.45; $p = 0.02$) and those with other types of tumor, 3.1-fold more odds of death (CI 95%, 1.58-6.24; $p = 0.001$).

DISCUSSION

MSCC is an anguishing manifestation associated with pain, progressive neurological decline and short-term dismal prognosis¹⁰. The present study concluded that patients with MSCC post-lung cancer had more odds of death when compared to patients with breast cancer, further to the evidence of the great impact this human dysfunction has. At the diagnosis, 55% of the patients were unable to do gait and at hospital discharge, 40% continued as such.

Other studies which addressed the patients' functionality showed the level of impairment that MSCC can cause¹⁵⁻¹⁷. According to Pessina et al.¹⁶, 42.3% of the patients with MSCC secondary to solid tumors were unable to do gait. Recently, Younsi et al.¹⁷ investigated the motor function pre and post-surgery of decompressive laminectomy in this population and reported that at admission, 80% of the patients did not ambulate and, at discharge, 51% recovered this ability.

Some aspects of MSCC are different from other medullary injuries of distinct etiology. Patients with traumatic medullary injuries are younger, with prolonged

Table 3. Estimate of post-MSCC survivorship time

Variable	Survivorship (%)			Median	Log-rank
	3 months	6 months	12 months		
Sex					
Male	55.6	37.0	22.2	3.6	0.15
Female	70.1	52.4	39.0	6.3	
Age at diagnosis of MSCC					
≤60 years	68.1	45.4	35.4	5.2	0.65
>60 years	58.5	54.4	28.2	6.1	
Ethnicity					
White	59.1	38.4	24.4	4.9	0.23
Other	67.9	52.3	38.0	6.2	
Marital status					
With spouse	66.7	49.2	32.9	5.9	0.68
Without spouse	63.5	47.0	35.0	4.7	
Education					
≤8 years	60.6	46.2	28.5	5.2	0.74
>8 years	68.2	50.1	41.7	6.3	
Types of primary tumor					
Breast	75.5	67.5	52.9	12.6	<0.001
Genitourinary	64.0	44.0	28.0	4.1	
Lung	52.5	13.1	00.0	3.1	
Other	46.2	15.4	7.7	2.6	
Segments affected					
Cervical	66.7	55.6	55.6	18.4	0.80
Thoracic	62.0	42.4	26.8	5.1	
Lumbosacral	78.6	35.7	35.7	5.2	
Multiple	64.3	50.0	42.9	3.7	
Types of treatment of MSCC					
Radiotherapy	64.3	47.7	34.8	5.4	0.54
Surgery	75.0	50.0	37.5	3.7	
Other	66.7	44.4	22.2	5.2	
Number of metastases before MSCC					
≤1 metastasis	68.3	52.4	36.0	6.2	0.23
>1 metastasis	62.6	42.3	31.2	4.5	
Liver metastasis					
Yes	66.7	47.6	35.7	5.1	0.81
No	65.4	47.6	33.3	5.4	
Number of vertebra affected					
≤2	66.7	54.9	39.0	6.3	0.04
>2	63.0	29.5	20.3	4.1	
Performance status					
≤2 vertebra	70.0	50.6	38.2	7.0	0.46
>2 vertebra	60.8	44.1	30.2	4.7	
Ambulation					
Yes	72.2	58.3	43.1	7.9	0.01
No	57.5	36.6	24.4	3.6	
Total	65.5	47.5	33.6	5.2	

Caption: MSCC = Metastatic spinal cord compression syndrome.

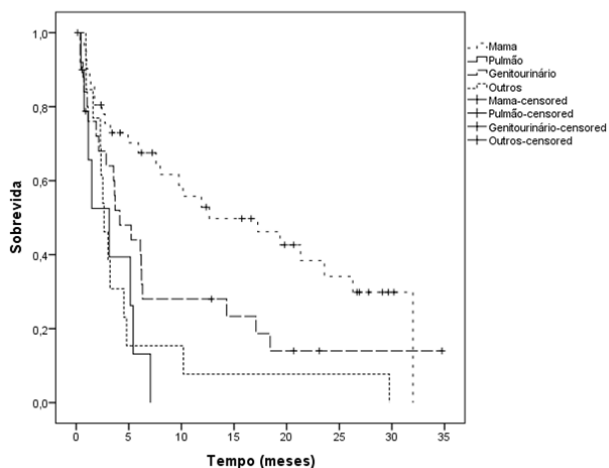


Chart 1. Survivorship of patients with SCMM according to the type of primary tumor

hospitalizations, higher proportion of complete medullary injuries, more compromise of cervical segment but with improvement of similar functionality when compared to patients with MSCC post-rehabilitation program^{18,19}.

There is higher proportion of tetraplegic patients in the group of non-traumatic medullary injuries compared with patients with MSCC, further to higher proportion of non-specificity of the anatomic level of the injury and similar improvement of the functionality in both groups post-rehabilitation program²⁰. These findings corroborate the data of the present study where only 20% of the patients had cervical compromise and just a few patients had complete medullary injuries (21%) at MSCC diagnosis. These data can be explained by the progressive nature of neurologic manifestations according to the tumor growth and medullary compression, facilitating the diagnosis before the injury is completed.

The results of the studies which addressed medullary injuries of different etiologies showed that, when well selected, patients with MSCC with higher life expectancy and participating in rehabilitation program improve functionality regardless of the etiological malignancy¹⁸⁻²⁰. In Brazil, the lack of information about prognostic factors of survival of patients with MSCC impact decision-making and management. In the present study, the type of primary tumor, the number of vertebra affected and ambulation were statistically significant survival factors, but after multiple analysis, only the primary tumor has shown to be an independent prognostic factor.

Previously, the prognostic impact of the type of primary tumor on the patients' survival with MSCC was referenced^{15,16,21-24}. Patients with breast and prostate cancer presented great life expectancy when compared to other types of cancer as lung cancer^{16,25,26} which corroborates the findings of this study where patients with MSCC

post-lung cancer had four-fold greater risk of dying when compared to patients with breast cancer.

Other variables as visceral metastases, ambulation ability and sex were widely discussed in studies which addressed MSCC^{24,27-30}. In a recent meta-analysis, it was suggested that visceral metastases is an important prognostic factor and has great impact on survivorship of patients with lung and prostate cancer²⁷. Another study demonstrated that women had substantially higher survival than men²⁸. In this study, the analysis of survival per sex did not present statistically significant findings, but it indicated that female patients had higher survival compared to male patients.

The ability to ambulate is a variable which demonstrated conflicting results in relation to patients' prognosis. In a multicenter study with patients submitted to radiotherapy, it was demonstrated that patients who did not ambulate before the first session of radiotherapy had more odds of early death²⁴. On the other hand, Feng et al. concluded that ambulation was a significant predictor of survivorship only in the univariate analysis, similar to the present study³⁰.

This study met an important knowledge gap in the national context. These new findings can help to identify patients with different diagnoses, allowing since more aggressive treatments to patients with better prognosis and counseling and supportive measures for patients with dismal prognosis focused to patient-centered decision-making. Only patients in physiotherapy follow-up were enrolled which may have been a selection bias, a possible limitation of the study. Nevertheless, the institutional routine recommends consultations to every patient with MSCC, reason for which although the bias is possible, it is believed it did not impact these results.

CONCLUSION

The type of primary tumor is an independent predictor factor for the survival of patients with MSCC, in addition of increased risk of death for patients with lung cancer when compared to breast cancer patients. At the diagnosis, furthermore, patients with MSCC are already with functioning loss and more than half of them with gait abnormality.

CONTRIBUTIONS

Gustavo Telles da Silva, Bianca Paraiso de Araujo and Eduarda Martins de Faria participated of the study design/conception, acquisition, analysis and interpretation of the data, wording and critical review. Patricia Almeida Chelles, Erica Alves Nogueira Fabro and Luciana Velasco Bizzo

participated of the study design/conception, wording and critical review. Luiz Claudio Santos Thuler, Alessandra Grasso Giglio and Anke Bergmann participated of the analysis and/or interpretation of the data, wording and critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

As the scientific-editor of INCA's "*Revista Brasileira de Cancerologia*" the author Anke Bergmann declares potential conflict of interests. The other authors have no conflict of interests.

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