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Clinical Study

Incidence, associated factors, and survival in metastatic spinal cord compression secondary to lung cancer

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Abstract

BACKGROUND CONTEXT: Bone metastasis (BM) occurs frequently in patients with lung cancer (LC). The most affected are the bones of the spine, increasing the risk of developing metastatic spinal cord compression (MSCC). Although MSCC is one of the most disabling complications, few studies have reported relevant results related to its frequency and prognosis among patients with LC.

PURPOSE: The purpose of this study was to determine the incidence and associated factors of the development of MSCC after BM with LC and its prognosis.

STUDY DESIGN/SETTING: This is a cohort study.

PATIENT SAMPLE: A cohort of 112 patients with BM because of LC, whose treatment was performed exclusively at the National Cancer Institute, was analyzed.

OUTCOME MEASURES: Study outcome measures included incidence of MSCC, factors associated with MSCC, and survival analysis.

METHODS: A cohort study was performed involving patients with BM because of LC diagnosed between 2007 and 2011. Clinical and sociodemographic data were extracted from the physical and electronic medical records because of initial diagnosis (up until December 2013). The association between the independent variables and the outcomes was performed by using crude and adjusted odds ratios (ORs), assuming 95% confidence intervals (CIs). For the exploratory evaluation between the independent variables and the time until the outcomes, Kaplan-Meier survival analysis was conducted. To identify if the differences between the curves were statistically significant, a log-tank test was calculated. A Cox multiple regression model, using the forward stepwise method, was applied, aiming to estimate the factors associated with time to death in the different exposure groups.

RESULTS: Of the 112 patients with BM, 31 (27.7%) developed MSCC. The univariate analysis showed that patients with three or more involved vertebrae revealed a 6.1 times greater risk of developing MSCC, compared with those with up to two metastatic vertebrae involved (OR: 6.1, 95% CI: 2.5–15.1, p<.001). Among the patients who developed MSCC, the median survival time was 4.4 months (95% CI: 1.5–7.3) and 4.7 months (95% CI: 3.5–5.9) in the patients without MSCC, not being a statistically significant difference (p=.19). After the occurrence of the MSCC, the median survival time was 2.8 months (95% CI: 1.4–4.1).

CONCLUSIONS: In this study, a high incidence of MSCC was observed in patients with BM. The study suggests that patients with three or more involved vertebrae per metastasis are more likely to develop MSCC. No alteration in the overall survival time was noticed among the patients with or without MSCC.

Keywords: Metastatic spinal cord compression; Lung cancer; Bone metastasis; Incidence; Associated factors; Survival

FDA device/drug status: Not applicable.

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EVIDENCE & METHODS

Context
While metastatic spinal cord compression (MSCC) is known to carry a poor prognosis in the setting of lung cancer, the incidence and epidemiology of this condition are not well described. The authors performed a cohort study involving patients with osseous metastasis from lung cancer treated at the Brazilian National Cancer Institute between 2007-2011.

Contribution
Nearly 28% of patients with osseous metastasis from lung cancer developed MSCC. Patients with metastases involving three of more vertebrae had the greatest odds of developing MSCC. As compared to individuals without MSCC, the development of cord compression did not significantly impact survival.

Implications
As a cohort study, this investigation suffers from the potential of selection as well as indication bias. There is also a limited sample and substantial treatment heterogeneity, with only one patient receiving surgical intervention by report, while two received no treatment whatsoever. Differences between the Brazilian and American health care systems may also limit the capacity to generalize this study's findings.

—The Editors

Introduction

Lung cancer (LC) is currently the most significant cause of cancer deaths in the world, and the number of new cases annually diagnosed remains high [1,2]. In Brazil, according to the Ministry of Health estimates for 2014, 16,400 new cases in men and 10,930 new cases in women are expected, representing crude incidence rates of 16.79 and 10.75 per 100 thousand, respectively [3].

The detection of LC, even with the advances in diagnostic technologies, normally occurs when the disease reveals an advanced stage locally, or the presence of metastasis, because symptoms in the early stages of the disease are not common [4]. Bone metastasis (BM) is observed in about 15% to 30% of the patients with LC, and this number may increase with the application of more sensitive diagnostic technologies [5,6]. The most affected are the bones of the spine, increasing the risk of developing Metastatic Spinal Cord Compression (MSCC) resulting in disability in mobility and causing poorer quality of life for patients [7–10]. Compared with other solid tumors such as breast cancer and prostate cancer, MSCC secondary to LC reveals a worse prognosis. The median survival time is 114 days in patients with prostate cancer, 74 days in patients with breast cancer, and 32 days in patients with LC [11–13].

Although MSCC is one of the most disabling complications, which leads to the risk of paralysis of the body structure below the lesion, few studies have reported results related to the frequency and prognosis among patients with LC. The identification of patients with a high risk of MSCC, beyond the knowledge of the factors associated with its occurrence and evolution, may help in understanding and planning collaborative strategies for the actions aimed at controlling this affliction. Therefore, the purpose of this study was to analyze the incidence, the associated factors, and the survival of patients with MSCC secondary to BM because of LC.

Methodology

A cohort study was carried out in all patients diagnosed with LC between 2007 and 2011, in which the treatment was performed exclusively at the Brazilian National Cancer Institute. Small-cell lung carcinoma (SCLC) (8040–8045) and non–small-cell lung carcinoma (NSCLC), including squamous cell carcinoma (8050–8076), adenocarcinoma (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8560, and 8570–8572) and large cell carcinoma (8012–8031 and 8310), were included. Clinical and sociodemographic data were extracted from the physical and electronic medical records from the initial diagnosis until December 2013. The evaluated variables were gender, age, race, marital status, schooling, history of smoking and alcohol consumption, histology, staging, body mass index, Eastern Cooperative Oncology Group Performance Status, number of involved vertebrae per metastasis, presence of other sites of BM, and treatment for the LC. The cutoff point of 60 years was used for age variable, according to the definition of World Health Organization, which considers, in developing countries, elderly as 60 years or older.

Although the histologic types SCLC and NSCLC have different characteristics in relation to risk and prognostic factors, it was used as a possible variable associated with occurrence of MSCC and overall survival. For the staging of the NSCLC, the stages I, II, III, and IV were considered. For the staging of the SCLC, the classifications used were limited disease and extensive disease. For the data analysis, early stage was considered Stage I to Stage IIIa for NSCLC and limited disease for SCLC. As for the advanced stage, stages IIIb and IV were considered for NSCLC and advanced disease for SCLC.

The MSCC was the time-dependent exposure variable of main interest, defined as indentation, displacement, or coating of the dural sac that surrounds the spinal cord or cauda equina by an extradural tumor mass [14]. The confirmation of the MSCC diagnosis was carried out through magnetic resonance imaging or spinal computed tomography.

A descriptive study of the population of the study was conducted using the central tendency and dispersion measures for the continuous variables and categorical frequency

distributions. The association between the independent variables and the outcomes was performed by using crude and adjusted odds ratios (ORs), assuming 95% confidence intervals (CIs).

For the exploratory evaluation between the independent variables and the time until the outcomes, a Kaplan-Meier method survival analysis was conducted. The patients lost during the follow-up and those who developed MSCC were considered censored. To identify if the differences between the curves were statistically significant, a log-rank test was calculated. A Cox multiple regression model using forward stepwise method was utilized, aiming to estimate the independent factors associated with death. The variables retained in the final model were used to adjust the risk of death associated with MSCC. For all the analyses, statistically significant p values were considered as $<.05$. Data were analyzed through SPSS software (Statistical Package for the Social Sciences for Windows), version 21.0.

This research was approved by the research ethics committee of the Brazilian National Cancer Institute (protocol 245/2013), being in accordance with the ethical principles established by the National Health Council, Resolution 466/12.

Results

Sociodemographic and clinical characteristics

The population of the study included 112 patients with BM secondary to LC, representing 18.5% of the total number of patients diagnosed with LC in the period of the study. The median age at diagnosis was 60.6 (standard deviation±8.8) years. Concerning the sociodemographic characteristics, the patients were predominantly men (60.7%), white (72.3%), married (66.1%), with a low level of education (63.4%), and had a history of smoking (88.4%) (Table 1).

For the diagnosis of LC, 27% were classified as overweight or obese, the majority being Eastern Cooperative Oncology Group Performance Status Stage I (65.2%). They were in advanced stages of LC, and most of the tumors were histologically classified as NSCLC (84.8%). The chemotherapy combined with radiotherapy was the most frequently eligible treatment (32.1%). The BM involved multiple locations, the spine (63.3%), ribs (32.1%), and pelvis (30.3%) being the most affected sites (Table 2).

The incidence of MSCC was 27.7% (31 patients); 16 patients (51.6%) had MSCC concomitantly with BM and 15 (48.4%) during the follow-up time. For these latter patients, the median time of developing MSCC was 1.3 months (95% CI: 0.6–2.0) (Fig. 1).

At the moment of the diagnosis of MSCC, 10 patients (32.5%) had no motor deficit, 7 (22.5%) had motor deficits but maintained walking capacity, 9 (29.0%) had severe motor deficit and not walking, and 5 (16.0%) had paraplegia.

Table 1
Sociodemographic characteristics of the population of the study (n=112)

Characteristics	Total (n=112) n (%)	NSCLC (n=95) n (%)	SCLC (n=17) n (%)
Gender			
M	68 (60.7)	58 (61.1)	10 (58.8)
F	44 (39.4)	37 (38.9)	7 (41.2)
Age to diagnosis (y)			
25–50	15 (13.4)	12 (12.6)	3 (17.6)
51–60	45 (40.2)	35 (36.8)	10 (58.9)
61–70	39 (34.8)	36 (37.9)	3 (17.6)
71–90	13 (11.6)	12 (12.7)	1 (5.9)
Race/color of the skin			
White	81 (72.3)	69 (72.6)	12 (70.6)
Brown	21 (18.8)	18 (18.9)	3 (17.6)
Black	6 (5.4)	5 (5.3)	1 (5.9)
No information	4 (3.6)	3 (3.2)	1 (5.9)
Marital status			
Married	74 (66.1)	62 (65.3)	12 (70.6)
Single	10 (8.9)	9 (9.5)	1 (5.9)
Widowed	11 (9.8)	11 (11.6)	0 (0)
Separated	14 (12.5)	11 (11.6)	3 (17.6)
No information	3 (2.7)	2 (2.1)	1 (5.9)
Schooling			
Illiterate	7 (6.3)	7 (7.4)	0 (0)
Elementary school	64 (57.1)	54 (56.8)	10 (58.8)
Secondary school	27 (24.1)	23 (24.2)	4 (23.5)
Higher education	10 (8.9)	8 (8.4)	2 (11.8)
No information	4 (3.6)	3 (3.2)	1 (5.9)
Smoking			
Yes	99 (88.4)	82 (86.3)	17 (100)
No	11 (9.8)	11 (11.6)	0 (0)
No information	2 (1.8)	2 (2.1)	0 (0)
Alcoholism			
Yes	58 (51.8)	51 (53.5)	7 (41.2)
No	38 (33.9)	31 (32.6)	7 (41.2)
No information	16 (14.3)	13 (13.7)	3 (17.6)

F, female; M, male; NSCLC, non–small-cell lung carcinoma; SCLC, small-cell lung carcinoma.

The most affected sites in MSCC were thoracic region (75.4%), lumbosacral (21.7%), and neck (2.9%). The treatment for MSCC was performed using radiotherapy in 28 patients (90.4%), 1 patient underwent surgery (3.2%), and 2 did not carry out any kind of treatment (6.4%).

Factors associated with the development of MSCC

Patients with three or more involved vertebrae revealed a 6.1 times greater risk of developing MSCC compared with those with up to two metastatic vertebrae involved (OR: 6.1, 95% CI: 2.5–15.1, $p<.001$). The remaining variables analyzed were not statistically associated with the occurrence of MSCC in the population (Table 3).

Survival time among patients with and without MSCC

The median survival time in patients with BM was 4.7 months (95% CI: 3.2–6.3). Among those who developed MSCC, the median survival time was 4.4 months (95% CI: 1.5–7.3) and 4.7 months (95% CI: 3.5–5.9) in patients

Table 2
Clinical characteristics of the population of the study (n=112)

Characteristics	Total (n=112) n (%)	NSCLC (n=95) n (%)	SCLC (n=17) n (%)
BMI			
Underweight	10 (8.9)	8 (8.4)	2 (11.8)
Eutrophic	48 (42.9)	43 (45.3)	5 (29.3)
Overweight/obese	31 (27.7)	23 (24.2)	8 (47.1)
No information	23 (20.5)	21 (22.1)	2 (11.8)
Performance status			
0	11 (9.8)	11 (11.6)	0 (0)
1	73 (65.2)	62 (65.3)	11 (64.7)
2	21 (18.8)	17 (17.9)	4 (23.5)
3	5 (4.5)	3 (3.2)	2 (11.8)
4	1 (0.9)	1 (1.1)	0 (0)
No information	1 (0.9)	1 (1.1)	0 (0)
Staging			
Initial	22 (19.6)	20 (21.1)	2 (11.8)
Advanced	79 (70.5)	71 (74.7)	8 (47.1)
Unknown	11 (9.8)	4 (4.2)	7 (41.2)
Histology			
SCLC	17 (15.2)	—	17 (100)
Adenocarcinoma	56 (50)	56 (58.9)	—
Squamous cell carcinoma	36 (32.1)	36 (37.9)	—
Large cell carcinoma	3 (2.7)	3 (3.2)	—
LC treatment			
Chemo+radio	36 (32.1)	30 (31.6)	6 (35.3)
Chemo	30 (26.8)	21 (22.1)	9 (52.9)
Radio	24 (21.4)	23 (24.2)	1 (5.9)
Surgery+chemo	10 (8.9)	10 (10.5)	0 (0)
Surgery	2 (1.8)	2 (2.1)	0 (0)
None	10 (8.9)	9 (9.5)	1 (5.9)
BM sites			
Spine	71 (63.3)	59 (62.1)	12 (70.5)
Ribs	36 (32.1)	31 (32.6)	5 (29.4)
Pelvis	34 (30.3)	23 (24.2)	11 (64.7)
Other	47 (41.9)	40 (42.1)	7 (41.1)

BM, bone metastasis; BMI, body mass index; chemo, chemotherapy; LC, lung cancer; NSCLC, non–small-cell lung carcinoma; radio, radiotherapy; SCLC, small-cell lung carcinoma.

without MSCC (Fig. 2). This difference is not statistically significant (p=.19).

After the occurrence of MSCC, the median survival time was 2.8 months (95% CI: 1.4–4.1). The Kaplan-Meier curve shows that 44.4% (95% CI: 26.7–62.1) of the patients survived more than 3 months, 26.9% (95% CI: 10.8–43) survived more than 6 months, and only 3.8% (95% CI: 0–11.2) survived more than 12 months (Fig. 3).

Estimates of time of survival after BM is presented (Table 4). The Cox analysis showed that better survival chances were associated with initial staging (p=.03), performance status 0–1 (p<.001), and realization of treatment for LC (p<.001). After the adjustments for these variables associated with overall survival, the Cox regression analysis revealed that there is no association between the presence of MSCC and the survival time after BM (OR: 1.05, 95% CI: 0.66–1.68).

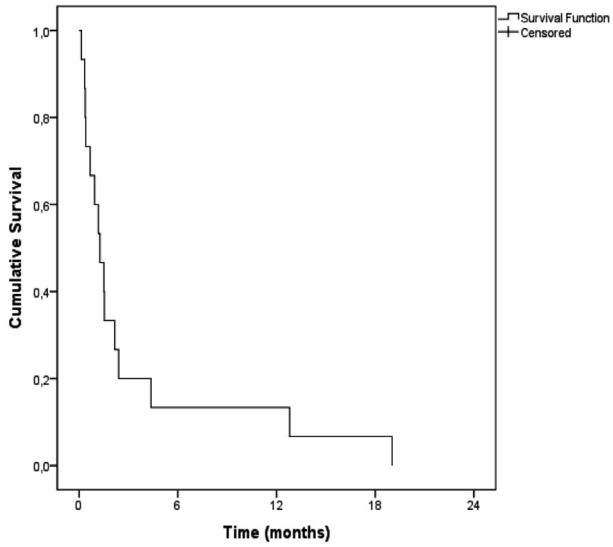

Fig. 1. Time between the bone metastasis and the metastatic spinal cord compression.

Discussion

In this study, 84.8% of the patients with BM had the non–small-cell histologic carcinoma type, which is compatible with the previous studies, which ranged between 82% and 91% [15,16]. Lung cancer has a high potential for turning into metastasis, and the skeletal system is frequently affected [16]. The LC diagnosis normally occurs in stages in which the disease has already progressed locally or systemically because the symptoms in the early stages of the disease are not common [4]. In this study, 70.5% of the patients with BM had the advanced stage of the disease at the moment of the diagnosis of LC. In a recent study [14], 41% of the patients had the disease distant at the time of diagnosis and, among them, 38% had BM during the first year after the cancer diagnosis.

After the development of BM, complications in the skeletal system may occur such as pathologic fractures, severe bone pain, hypercalcemia, and MSCC [17]. MSCC is the most disabling complication that may show sparse initial symptoms, and it may progress to loss of function below the level of the lesion [18,19]. The incidence of MSCC after BM was 27.7%. As far as we know, this is the first study that describes the incidence of MSCC after BM in patients with LC. Previous studies [20,21] performed in other countries included only patients with breast cancer and prostate cancer. In the study by Venkitaraman et al. [20], there were 150 patients with BM after prostate cancer and 27.3% revealed radiological evidence of MSCC. In the study by Plunkett et al. [21], of the 243 patients that had BM after breast cancer, 15% developed MSCC. The median time for developing MSCC after BM was 4.4 and 15.5 months in patients with breast cancer and prostate cancer, respectively [22,23]. On the other hand, the median time between BM and MSCC in patients with LC in this study was only 1.3 months.

Table 3
Factors associated to the development of MSCC after BM in patients with LC

Characteristics	MSCC		OR (95% CI)	p Value
	Yes	No		
Gender				
M	18 (58.1)	50 (61.7)	Reference	
F	13 (41.9)	31 (38.3)	1.2 (0.5–2.7)	.72
Age to prognosis (y)				
>60	14 (45.2)	38 (46.9)	Reference	
≤60	17 (54.8)	43 (53.1)	1.1 (0.5–2.5)	.86
Race/skin color				
White	19 (63.3)	62 (79.5)	Reference	
Non-white	11 (36.7)	16 (20.5)	2.2 (0.9–5.7)	.09
Marital status				
With partner	17 (56.7)	57 (72.2)	Reference	
Without partner	13 (43.3)	22 (27.8)	2.0 (0.8–4.7)	.12
Schooling				
≤8 y of study	15 (50)	45 (57.7)	Reference	
>8 y of study	15 (50)	33 (42.3)	1.4 (0.6–3.2)	.47
Smoking				
Yes	31 (100)	68 (86.1)	NA	.08
No	0 (0)	11 (13.9)		
Alcoholism				
Yes	12 (46.2)	43 (65.7)	Reference	
No	14 (53.8)	24 (34.3)	2.2 (0.9–5.6)	.09
Histology				
NSCLC	24 (77.4)	71 (87.7)	Reference	
SCLC	7 (22.6)	10 (12.3)	2.1 (0.7–6.0)	.18
Staging				
Initial	3 (10.7)	19 (26)	Reference	
Advanced	25 (89.3)	54 (74)	2.9 (0.8–10.8)	.10
BMI				
Overweight or obese	10 (33.3)	21 (35.6)	Reference	
Underweight or normal weight	20 (60.7)	38 (64.4)	1.1 (0.4–2.8)	.83
Performance status				
0–1	23 (74.2)	61 (76.2)	Reference	
≥2	8 (25.8)	19 (23.8)	1.1 (0.4–2.9)	.82
Number of involved vertebrae				
<3	13 (41.9)	66 (81.5)	Reference	
≥3	18 (58.1)	15 (18.5)	6.1 (2.5–15.1)	*<.001*
Other BM				
No	16 (51.6)	50 (61.7)	Reference	
Yes	15 (48.4)	31 (38.3)	1.5 (0.6–3.5)	.33
LC treatment				
Surgery or surgery+chemo	2 (6.5)	10 (12.3)	Reference	
Chemo, radio, chemo+radio	24 (77.4)	66 (81.5)	1.8 (0.4–8.9)	.46
None	5 (16.1)	5 (6.2)	5.0 (0.7–35.5)	.10

BM, bone metastasis; BMI, body mass index; chemo, chemotherapy; CI, confidence interval; F, female; LC, lung cancer; M, male; MSCC, metastatic spinal cord compression; NA, not applicable; NSCLC, non–small-cell lung carcinoma; OR, odds ratio; radio, radiotherapy; SCLC, small-cell lung carcinoma.

Note: The statistically significant values are highlighted in italics.

Knowing the predictors for the development of MSCC is important for the planning of prevention and control strategies. In this study, it was shown that the number of vertebrae involved in metastasis is significantly associated with the probability of developing MSCC. This association is supported by the previous reports of primary prostate cancer studies [20,24]. In the study by Godman et al. [25], there were 616 patients with LC and 24 (4%) developed MSCC. Cerebral metastasis and positive bone scan gave a 25% chance of developing MSCC. In a recent systematic review that approached the identification of patients with high risk of MSCC for several types of primary tumors, it was suggested that the more spinal metastases present and the longer the patient is at risk, the higher is the chance of developing MSCC and a higher risk if they already present BM [26].

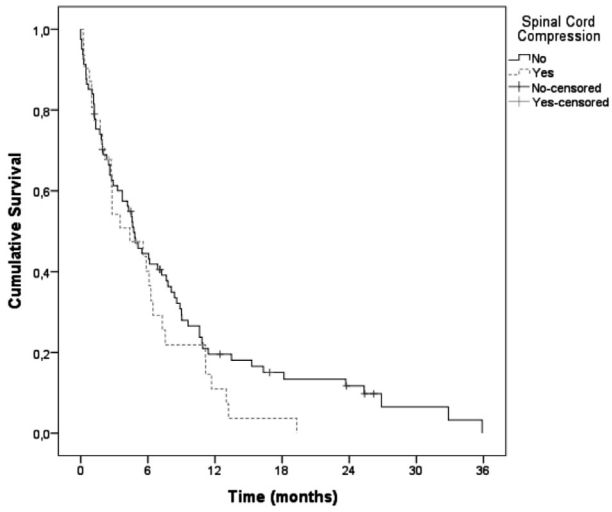

Fig. 2. Overall survival among patients with and without metastatic spinal cord compression.

This study confirms the severity of BM in patients with LC. The median survival time in patients with BM without MSCC was 4.7 month and in patients with BM and MSCC was 4.4 months. There was no statistically significant difference between these groups. In a prospective study [15] of 554 patients with BM after LC, a similar

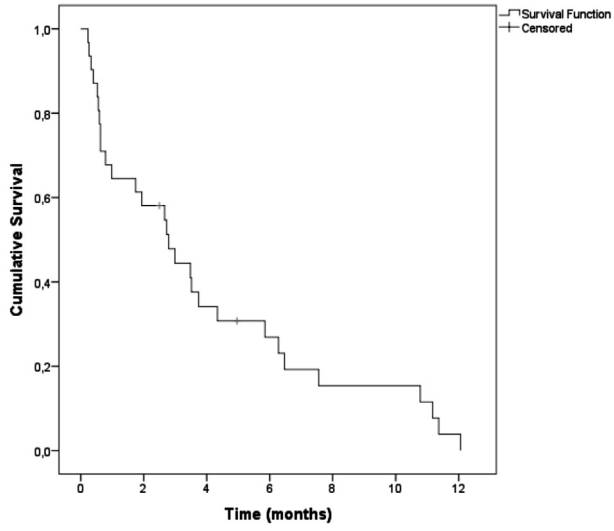

Fig. 3. Time between the metastatic spinal cord compression and death.

Table 4
Estimates of time of survival after BM

Variable	No. of events	Time of survival Median (95% CI)	Log rank*
Gender			
M	61	4.5 (2.5–6.5)	.82
F	39	5.6 (3.5–7.7)	
Age to diagnosis (y)			
>60	58	4.2 (2.2–6.1)	.32
≤60	42	5.5 (3.7–7.5)	
Race/skin color			
White	73	4.6 (2.7–6.6)	.79
Non-white	23	2.9 (1.1–4.7)	
Marital status			
With partner	67	4.4 (3.1–5.8)	.87
Without partner	30	5.5 (2.9–7.9)	
Schooling			
≤8 y of study	51	3.7 (1.9–5.5)	.34
>8 y of study	45	6.8 (4.7–9.0)	
Smoking			
Yes	89	4.8 (3.5–6.1)	.53
No	9	4.2 (0.5–7.8)	
Alcoholism			
Yes	50	3.7 (1.8–5.6)	.93
No	34	5.6 (3.4–7.8)	
Histology			
NSCLC	83	4.7 (3.0–6.9)	.37
SCLC	17	4.5 (1.3–7.8)	
Staging			
Initial	17	8.1 (2.6–13.6)	*.03*
Advanced	73	4.4 (2.3–6.4)	
BMI			
Underweight or normal weight	52	4.8 (4.0–5.7)	.34
Preobese or obese	27	6.1 (1.0–11.3)	
Performance status			
0–1	43	8.6 (5.9–11.2)	*<.001*
≥2	51	2.7 (1.2–4.3)	
Number of involved vertebrae			
<2	71	4.3 (3.0–5.6)	.76
≥3	29	5.8 (4.8–6.9)	
Other BM			
Yes	41	4.9 (3.0–6.7)	.88
No	59	3.7 (1.4–6.0)	
LC treatment			
None	9	1.9 (0.1–4.0)	*<.001*
Chemo, radio, chemo+radio	83	4.6 (2.9–6.3)	
Surgery and surgery+chemo	8	13.5 (5.1–21.8)	

BM, bone metastasis; BMI, body mass index; chemo, chemotherapy; CI, confidence interval; LC, lung cancer; NSCLC, non–small-cell lung carcinoma; radio, radiotherapy; SCLC, small-cell lung carcinoma.

Note: The statistically significant values are highlighted in italics.

* Calculated only with the known values.

result to our study was demonstrated. There was no statistically significant difference in the survival of the patients with BM without skeletal-related events (6 months) versus patients with BM and skeletal-related events (5.3 months). In this study, skeletal-related events were considered as the presence of MSCC, pathologic fractures, and hypercalcemia.

Concerning the prognosis of MSCC after LC, several studies show shorter survival times compared with other types of solid tumors, such as breast and prostate [8,12,27–30]. Before 2007, the studies related to patients with MSCC after LC reported a survival time ranging between 30 and 40 days [12,19,31]. In the present study, which analyzed patients with MSCC after LC between 2007 and 2011, there was a better prognosis, where 44.4% of the patients survived for more than 3 months, 26.9% survived for more than 6 months, 3.8% survived for more than 12 months, and the time of median survival was 2.8 months. In two recent studies, better results were observed. Rades et al. [32,33] studied 356 cases of MSCC secondary to NSCLC between 1992 and 2010 and described survival times of 6 and 12 months at 28% and 14%, respectively; the median survival time was 4 months. Yet, Morgen et al. [34] demonstrated that the survival time of 12 months in patients with MSCC secondary to LC revealed a statistically significant increase between 2005 and 2010, ranging from 4% to 19%. These recent results revealed an improvement in the prognosis of this population. However, it's important to be cautious when reading these results because the survival times in patients with advanced LC may be increasing because of the incorporation of new therapeutic options, including specific treatments for specific molecular targets [35].

In conclusion, in the present study, a high incidence of MSCC was observed in patients with BM. The study suggests that patients with more than three involved vertebrae per metastasis are more likely to develop MSCC. No survival differences were observed in patients with or without MSCC.

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