

ORIGINAL ARTICLE

Predictors of overall survival in non-small-cell lung cancer patients with metastatic spinal cord compression treated with short-course radiotherapy

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Abstract

Metastatic spinal cord compression (MSCC) is a condition that impacts directly on the patient's prognosis.

Objective: The study purpose was to identify predictors of overall survival in non-small-cell lung cancer (NSCLC) patients with MSCC.

Methods: A cohort study involving NSCLC patients enrolled between 2008 and 2017 was performed. Sixty-four patients treated with short-course radiotherapy were included. Clinical and socio-demographic data were extracted from medical records. Data were analysed using survival analysis and Cox proportional hazard regression analysis.

Results: The median survival time was 2.5 months (95% CI: 1.6–3.5). Patients >60 years had shorter survival than younger patients (HR 1.85; 95% CI 1.06–3.24; $p = 0.02$), and patients with performance status (PS) >2 had shorter survival than those with PS ≤ 2 (HR 1.93; 95% CI 1.12–3.33; $p = 0.01$).

Conclusion: This study found worse PS and higher age are independent predictors of overall survival in NSCLC patients with MSCC treated with short-course radiotherapy after adjusting the potential confounding factors (PS, age and target therapy).

KEYWORDS

metastatic spinal cord compression, non-small-cell lung cancer, predictors, radiotherapy, short-course, survival

1 | INTRODUCTION

Lung cancer (LC) is one of the most common cancers in the world (Siegel et al., 2018). Since LC symptoms rarely occur at an early stage, their diagnosis is usually obtained when the disease has already progressed locally or when metastasis is already present (Riihimäki et al., 2014). Therefore, mortality rates remain high in the male and female populations (Bray et al., 2018).

Lung cancer is usually categorised into two groups: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). NSCLC

is responsible for about 85% of all LC cases (Sathiakumar et al., 2013). One of the most common sites of metastasis in NSCLC patients is the skeletal system (Riihimäki et al., 2014). Approximately 28% of patients with bone metastasis develop metastatic spinal cord compression (MSCC), and the risk increases with the number of affected or compromised vertebrae (Silva et al., 2015a, 2015b; Sutcliffe et al., 2013).

Metastatic spinal cord compression is considered a complication of high importance in the morbidity of cancer patients and may cause pain, paralysis of body structures below the level of

metastasis, and urinary and faecal incontinence, negatively affecting their quality of life and prognosis (Campillo-Recio et al., 2019; Duran et al., 2017; Morgen et al., 2016). Treatment of this complication includes the use of analgesics, corticosteroids, chemotherapy, radiotherapy and surgery, these modalities being administered alone or in combination with other therapies. However, many MSCC patients are often treated with isolated radiotherapy (Gutt et al., 2018; Morten et al., 2018; Silva et al., 2015a, 2015b). Short-course radiotherapy in 1 week or less promotes less discomfort, requires a shorter treatment time and is considered appropriate for patients with a limited life expectancy (Lutz et al., 2011; Rades et al., 2011, 2014).

After the diagnosis of MSCC in LC patients, several studies have shown shorter survival when compared to other types of solid tumours (Conway et al., 2007; Morgen et al., 2013; Tabouret et al., 2015). The 1-year survival in MSCC is 19% in LC patients, 20% in prostate cancer patients and 50% in breast cancer patients (Morgen et al., 2013). In NSCLC patients treated with short-course radiotherapy and conventional treatments, the median survival time is 4 months (Rades et al., 2012).

Although MSCC is a condition that is difficult to control and negatively impacts on the patient's quality of life, prognostic factors have not been well described in patients with NSCLC. Knowledge of prognostic factors for survival in patients undergoing palliative treatment will be useful for understanding the evolution of this condition, enabling the optimisation of supportive measures and treatment customisation. Therefore, the purpose of this study is to analyse independent predictors of overall survival in NSCLC patients with MSCC treated with short-course radiotherapy.

2 | METHODOLOGY

A retrospective cohort study was conducted in patients diagnosed with NSCLC between January 2008 and December 2017, whose treatment planning and implementation was performed exclusively in a cancer centre (Brazilian National Cancer Institute—INCA).

Sixty-four patients with MSCC who received short-course radiotherapy (8 Gy \times 1 or 20 Gy \times 5) alone were included. The treatment included at least one vertebra above and below the affected vertebra. Patients with previous neurological diseases who had had previous surgery to treat MSCC were excluded from the study.

Metastatic spinal cord compression was defined as dorsal sac indentation, displacement or lining involving the spinal cord or equine tail by extradural tumour mass (Loblaw Da & Laperriere, 1998). Confirmation of the diagnosis of MSCC was performed by magnetic resonance imaging or computed tomography, according to the hospital routine.

Clinical and socio-demographic data were extracted from physical and electronic medical records. The variables extracted were sex, age, ethnicity, education, histology, body mass index (BMI), performance status (PS), number of vertebrae affected by metastasis, target therapy, visceral metastasis, number of metastases in other organs and time interval from NSCLC diagnosis to MSCC.

The outcome evaluated was overall survival, being defined as the time elapsed between the diagnosis of MSCC until the event (death) or the last visit to the hospital (censorship). The follow-up of patients was 12 months.

This study was approved by the Research Ethics Committee of the Brazilian National Cancer Institute (protocol CAAE: 89670418.0.00000.5274, approval number 2.714.857/2018).

2.1 | Statistical analysis

A descriptive study of the study population was performed, using measures of central tendency and dispersion for continuous variables and frequency distributions for categorical variables. Survival analysis was performed using the Kaplan–Meier method, and the differences between the curves were done by log-rank test. For adjust potential confounding factors, variables with $p < 0.20$ in the univariate analysis were included in the multivariate model in a forward stepwise manner in order to estimate the independent variables (predictors) and the dependent variable (survival). For all analyses, p value < 0.05 was considered statistically significant. Data were analysed using SPSS software (Statistical Package for Social Science for Windows) version 21.0.

3 | RESULTS

3.1 | Socio-demographic and clinical characteristics

The study population consisted of 64 NSCLC patients with MSCC, with a mean age at diagnosis of 60.6 years (± 9.5). Regarding socio-demographic characteristics, the patients were predominantly men (54.7%), white (56.3%), ≤ 60 years (51.6%) and with a low level of education (53.1%). Patients predominantly had PS > 2 (59.4%) and were in the stage IV at the time of NSCLC diagnosis (82.8%). The most common histological types were adenocarcinoma (62.5%) and squamous cell carcinoma (23.4%) (Table 1). The vertebral segments most commonly affected by MSCC were the thoracic spine (69.7%) and lumbar spine (20.2%).

At the time of the diagnosis of MSCC, 33 patients (51.6%) had sphincter dysfunction, 17 patients (26.6%) had no motor deficit, 15 patients (23.4%) had motor deficit, but walking ability was preserved, 17 patients (26.6%) had severe motor deficits and were not walking, and 13 patients (20.3%) had paraplegia. As support measures, 50 patients (78.1%) performed physiotherapy sessions during hospitalisation, 22 patients (34.4%) used adapted orthoses for pain relief and spinal stabilisation, and 34 patients (53.1%) were directed to palliative care (Table 1).

After the occurrence of MSCC, the median survival time was 2.5 months (95% CI: 1.5–3.5). Survival rates were 41.5% at 3 months, 22.2% at 6 months and 5.6% at 12 months. Estimates of overall survival according to demographic and clinical characteristics are presented in Table 2.

TABLE 1 Socio-demographic and clinical characteristics of the study population ($n = 64$)

Characteristics	n (%)
Gender	
Male	35 (54.7%)
Female	29 (45.3%)
Age at diagnosis of MSCC	
≤ 60 years	33 (51.6%)
> 60 years	31 (48.4%)
Ethnicity	
White	36 (56.3%)
Others	27 (42.2%)
Missing in records	1 (1.5%)
Years of education	
≤ 8 years of study	34 (53.1%)
> 8 years of study	29 (45.3%)
Missing in records	1 (1.6%)
Stage	
III	9 (14.1%)
IV	53 (82.8%)
Missing in records	2 (3.1%)
Body Mass Index	
Eutrophic	33 (58.9%)
Others	23 (41.1%)
Missing in records	8 (12.5%)
Performance status	
≤ 2	26 (40.6%)
> 2	38 (59.4%)
Number of involved vertebrae	
≤ 2	39 (61.0%)
> 2	25 (39.0%)
Histology	
NSCLC not specified	7 (10.9%)
Adenocarcinoma	40 (62.6%)
Squamous Cell Carcinoma	15 (23.4%)
Large Cell Carcinoma	2 (3.1%)
Target therapy	
Yes	11 (17.2%)
No	53 (82.8%)
Visceral metastasis	
Yes	17 (26.6%)
No	47 (73.4%)
Other bone metastasis	
Yes	27 (42.2%)
No	37 (57.8%)
Interval from NSCLC diagnosis to MSCC	
> 12 months	10 (15.6%)
≤ 12 months	54 (84.4%)

(Continues)

TABLE 1 (Continued)

Characteristics	n (%)
Sphincter dysfunction	
Yes	33 (51.6%)
No	25 (39.1%)
Missing in records	6 (9.4%)
Physiotherapy	
Yes	50 (78.1%)
No	14 (21.9%)
Orthoses	
Yes	22 (34.4%)
No	42 (65.6%)
Palliative care	
Yes	34 (53.1%)
No	30 (46.9%)
RT fractionation regimen	
8 Gy \times 1	36 (56.2%)
4 Gy \times 5	28 (43.8%)
Diagnostic period	
2008–2012	41 (64.1%)
2013–2017	23 (35.9%)

Abbreviations: MSCC, Metastatic spinal cord compression; NSCLC, non-small-cell lung cancer; RT, radiotherapy.

In Kaplan–Meier analysis, among patients with PS ≤ 2 , the median survival time was 3.4 months (95% CI 2.0–4.9) and in those with PS > 2 it was 1.3 months (95% CI, 1.0–1.7) ($p = 0.03$) (Figure 1). Among younger patients (≤ 60 years), median survival time was 3.1 months (95% CI, 2.07–4.23) and 1.4 months (95% CI, 1.0–1.88) in elderly patients (> 60 years) ($p = 0.05$) (Figure 2). The 12-month survival rates were 2.6% for patients diagnosed between 2008 and 2012 and 6.2% for patients diagnosed between 2013 and 2017. Insignificant increase in overall survival was observed between two studied periods ($p = 0.43$).

The variables with $p < 0.20$ in the univariate analysis of prognostic factors were included in the multiple regression model (Table 3).

In Cox multiple regression analysis, patients > 60 years had shorter survival than those ≤ 60 years (HR 1.85; 95% CI 1.06–3.24; $p = 0.02$), and patients with PS > 2 had shorter survival than those with PS ≤ 2 (HR 1.93; 95% CI 1.12–3.33; $p = 0.01$) after adjusting the potential confounding factors (PS, age and target therapy) (Table 4).

4 | DISCUSSION

This study showed a short life expectancy in NSCLC patients with MSCC. Variables such as age and PS influenced the survival of this population.

Metastatic spinal cord compression is a serious complication of LC that can lead to loss of neurological functions below the level of

TABLE 2 Estimates of survival time in MSCC patients

Variable	Survival Rate (%)			Median survival (months)	Log Rank (p Value)
	3 months	6 months	12 months		
Gender					
Male	38.8	12.9	3.2	1.9	0.26
Female	44.9	32.9	8.2	2.5	
Age at diagnosis of MSCC					
≤60 years	50.4	28.4	6.3	3.1	0.05
>60 years	30.8	15.4	5.1	1.4	
Ethnicity					
White	41.5	23.3	0.0	1.9	0.36
Others	43.2	21.5	12.9	2.7	
Years of education					
≤8 years of study	41.2	17.2	10.3	2.6	0.32
>8 years of study	39.3	24.5	0.0	2.3	
Stage					
III	33.3	22.2	0.0	1.1	0.75
IV	44.7	23.2	7.0	2.5	
Body Mass Index					
Eutrophic	42.5	24.8	3.5	2.5	0.92
Others	41.4	17.3	5.8	1.5	
Performance status					
≤2	61.5	34.2	4.3	3.4	0.03
>2	26.5	13.8	6.5	1.3	
Histology					
Adenocarcinoma	42.4	23.6	2.9	2.3	0.79
Non-Adenocarcinoma	39.8	19.9	9.9	2.5	
Number of involved vertebrae					
≤2	34.4	19.8	5.7	1.9	0.83
>2	53.5	25.5	5.1	3.0	
Target therapy					
Yes	54.5	45.5	11.4	4.3	0.06
No	38.7	17.2	4.3	1.9	
Visceral metastasis					
Yes	48.2	41.4	0.0	2.7	0.68
No	39.1	15.2	7.1	2.3	
Other bone metastasis					
Yes	50.4	31.0	7.8	3.0	0.35
No	34.4	15.0	0.3	2.5	
Interval from NSCLC diagnosis to MSCC					
>12 months	30.3	15.4	0.0	1.2	0.44
≤12 months	43.9	23.5	6.3	2.6	
Sphincter dysfunction					
Yes	35.0	19.5	0.5	1.8	0.64
No	48.0	27.4	0.0	2.7	

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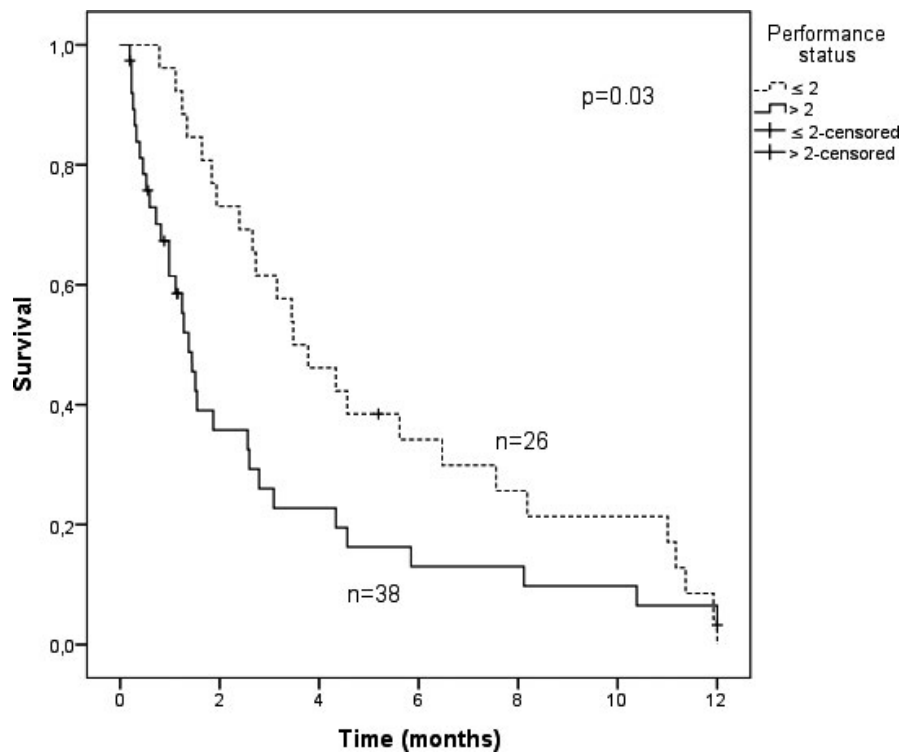
TABLE 2 (Continued)

Variable	Survival Rate (%)			Median survival (months)	Log Rank (p Value)
	3 months	6 months	12 months		
Physiotherapy					
Yes	39.9	19.9	0.6	1.9	0.87
No	47.1	23.6	11.8	2.6	
Orthoses					
Yes	50.3	30.2	0.0	3.0	0.97
No	36.8	17.7	0.6	1.6	
Palliative care					
Yes	50.0	26.5	0.5	2.7	0.32
No	30.7	15.8	0.5	1.4	
RT fractionation regimen					
8 Gy × 1	40.2	22.7	3.3	2.3	0.48
4 Gy × 5	42.6	21.4	8.6	2.5	
Diagnostic period					
2008–2012	36.2	20.7	2.6	1.8	0.38
2013–2017	51.4	24.7	6.2	3.0	
Total	41.5	22.2	5.6	2.5	

Note: In bold, statistically significant difference.

Abbreviations: MSCC, Metastatic spinal cord compression; NSCLC, non-small-cell lung cancer; RT, radiotherapy.

FIGURE 1 Survival time of patients with metastatic spinal cord compression according to performance status



the lesion. Even with the acute neurological deficits that patients have, there is few recommendation for surgical treatment due to the potential risks of complications and short life expectancy (Chen et al., 2007; Da silva et al., 2017; Park et al., 2016).

At MSCC diagnosis, 33% of NSCLC patients were not walking, about 90% of cases received radiotherapy and approximately 10% of patients underwent surgery (Da silva et al., 2017). Due to the poor prognosis, isolated radiotherapy seems to be the most reasonable

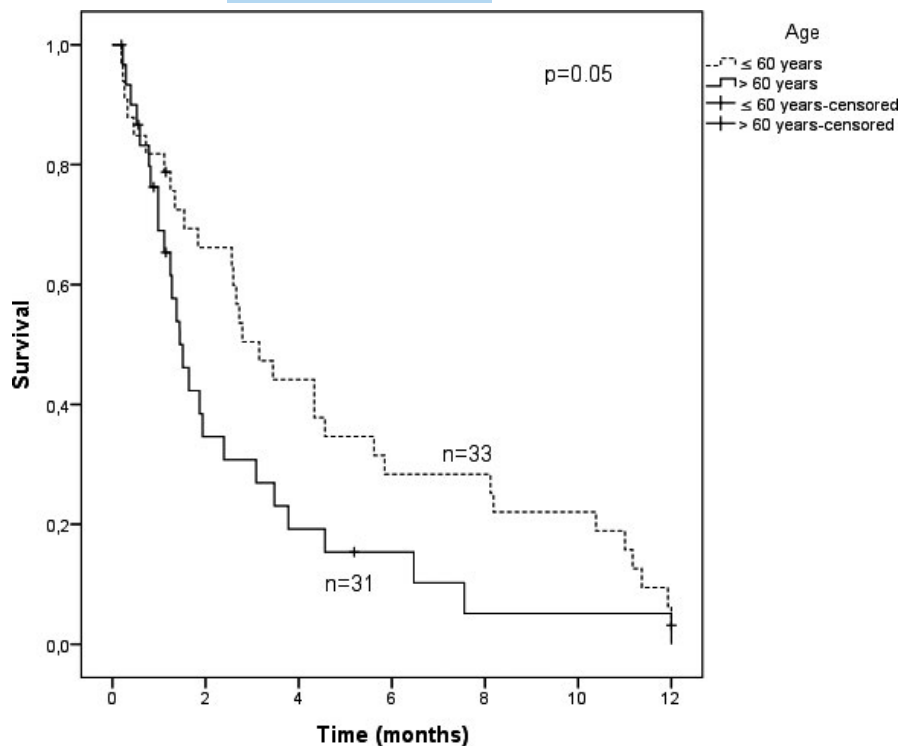


FIGURE 2 Survival time of patients with metastatic spinal cord compression according to age

option. As each treatment session can be associated with discomfort for the often debilitated patients with severe pain and decreased functionality, the treatment time should be as short as possible (Rades et al., 2013).

Recently, several studies have addressed different radiotherapy regimens for the treatment of MSCC (Giraldo et al., 2017; Rades, Conde-Moreno, Cacicedo, Segedin, et al., 2018; Rades, Conde-Moreno, Cacicedo, Veninga, et al., 2018). Rades, Conde-Moreno, Cacicedo, Veninga, et al. (2018) compared two radiotherapy regimens (1×8 Gy vs 5×4 Gy) in patients with MSCC and poor, intermediate and favourable prognoses. In the poor prognosis group, the most frequent primary tumour was lung cancer ($n = 46$), and there was no significant difference in 6-month survival between the radiotherapy regimens. In a randomised clinical trial comparing two radiotherapy regimens (5×4 Gy vs 10×3 Gy) in patients with MSCC, it was shown that treatment with 5×4 Gy was non-inferior when compared to 10×3 Gy in the poor and intermediate prognosis groups (Rades, Conde-Moreno, Cacicedo, Segedin, et al., 2018). According to a meta-analysis, treatment with conventional and short-course radiotherapy for MSCC has similar results for both survival and functionality, but conventional irradiation had better results for local control (Qu et al., 2015). In the current study, which evaluated NSCLC patients with MSCC treated with short-course radiotherapy, the survival rate was 41.5% at 3 months, 22.2% at 6 months and 5.6% at 12 months. In a prospective study that jointly analysed MSCC patients with short life expectancy treated with 1×8 Gy, the survival at 3 and 6 months was 14.3% and 8.6%, respectively, and the median survival time was 1.5 months with a moderate response to pain. The most frequent primary tumour in these patients with MSCC was LC (40%) (Giraldo et al., 2017). In a study by Rades et al.

(2012), a series of 356 cases of NSCLC secondary to MSCC between 1992 and 2010 treated exclusively with short-course and conventional radiotherapy was studied, and survival at 6 and 12 months of 28% and 14%, respectively, was described.

In this study, prognostic factors for survival in NSCLC patients with MSCC were evaluated. Patients >60 years and with PS >2 had worse survival. Other studies addressed prognostic factors in LC patients with MSCC and, in a multivariate analysis, identified some similar and other discordant prognostic factors. Rades et al. selected only elderly patients with LC who were treated for MSCC by radiotherapy and identified that poor PS (>2), development of rapid motor deficit, presence of visceral metastasis and inability to walk were associated with poor survival. Chen et al. (2007), in a series of NSCLC patients who underwent palliative surgery for MSCC, identified that shorter survival was associated with PS. A retrospective study that evaluated 120 SCLC patients between 1996 and 2016 found that the time interval between SCLC and treatment with radiotherapy, visceral metastasis, PS and ambulatory status was associated with poor survival. A multicentre study that evaluated only NSCLC patients with MSCC showed that male gender, poor PS (>2), inability to walk prior to radiotherapy, involvement of many vertebrae by metastasis, presence of visceral metastases, other bone metastases, short time interval between NSCLC diagnosis and MSCC radiotherapy and the development of fast motor deficit were independent factors associated with worse prognosis. Unlike other research, this study did not show a positive association for the variables usually discussed in the literature, such as visceral metastasis. The non-identification of statistical significance can be attributed to the different population of patients who underwent only short-course radiotherapy to treat MSCC and the small number of study

TABLE 3 Univariate analysis of prognostic factors for non-small-cell lung cancer patients with metastatic spinal cord compression

	HR	95% CI	p Value
Gender			
Female	1.34	Reference	0.27
Male		0.79–2.28	
Age at diagnosis of MSCC			
≤60 years	1.66	Reference	0.06
>60 years		0.97–2.84	
Ethnicity			
Others	1.28	Reference	0.37
White		0.74–2.23	
Years of education			
≤8 years of study	1.31	Reference	0.33
>8 years of study		0.75–2.27	
Stage			
IV	1.19	Reference	0.63
III		0.57–2.45	
Body Mass Index			
Others	1.02	Reference	0.92
Eutrophic		0.57–1.82	
Performance status			
≤2	1.76	Reference	0.03
>2		1.03–2.99	
Histology			
Non-Adenocarcinoma	1.07	Reference	0.79
Adenocarcinoma		0.62–1.84	
Number of involved vertebrae			
>2	1.05	Reference	0.83
≤2		0.61–1.81	
Target therapy			
Yes	1.91	Reference	0.07
No		0.93–3.92	
Visceral metastasis			
No	1.18	Reference	0.69
Yes		0.50–2.80	
Other bone metastasis			
No	1.28	Reference	0.35
Yes		0.75–2.18	
Interval from NSCLC diagnosis to MSCC			
≤12 months	1.32	Reference	0.44
>12 months		0.64–2.71	
Sphincter dysfunction			
No	1.26	Reference	0.40
Yes		0.72–2.21	

(Continues)

TABLE 3 (Continued)

	HR	95% CI	p Value
Physiotherapy			
Yes	1.05	Reference	0.87
No		0.55–2.01	
Orthoses			
No	1.00	Reference	0.97
Yes		0.57–1.76	
Palliative care			
Yes	1.30	Reference	0.33
No		0.76–2.21	
RT fractionation regimen			
4 Gy × 5	1.20	Reference	0.48
8 Gy × 1		0.70–2.06	

Note: In bold, statistically significant p value.

Abbreviations: CI, confidence interval; HR, hazard ratio.

participants. On the other hand, similar to our study, Nenclares (2019) demonstrated that patients older than 60 years, with worse PS, a higher number of vertebrae involved, and tumours with unfavourable prognosis such as LC are predictive factors for worse survival in patients with MSCC.

In recent years, several studies have been directed towards the creation of scores to predict survival and to help in the selection of individualised therapeutic strategies in LC patients with MSCC (Rades et al., 2012; Rades et al., 2016; Rades et al., 2019). However, few studies address MSCC patients with short life expectancy who may be candidates for the best supportive care. In 2019, Nenclares et al. created a score based on 138 patients with MSCC treated with isolated radiotherapy to simplify and facilitate the decision to choose between a short and long-course radiotherapy regimen. In a retrospective study involving 2029 patients with MSCC caused by different tumour types, a scoring system was developed to identify patients who could be candidates for the best supportive care or single-dose radiotherapy. The study showed that 32% of LC patients with MSCC died within 2 months, the highest percentage among all tumour types studied (Rades et al., 2013). In our study, NSCLC patients had a limited life expectancy of 2.5 months, and 58.5% died within 3 months. For this selected group of patients, intensive treatments leading to over-treatment should be avoided, and the use of corticosteroids and analgesics could be a reasonable option. Patients with MSCC need comprehensive physical, psychological and social care. According to Santos et al. (2018), palliative rehabilitation should be integrated early, and strategies should be directed according to patients' prognosis.

In the present study, patients diagnosed between 2008 and 2012 had 12-month survival rates of 2.6%, and those diagnosed between 2013 and 2017 had a 12-month survival rate of 6.2%. However, despite this time difference, the survival rate was not statistically significant between periods ($p = 0.43$) thus, suggesting insignificant

TABLE 4 Multiple analysis of prognostic factors for non-small-cell lung cancer patients with metastatic spinal cord compression

	HR	95% CI	p Value
Age			
>60 years vs. ≤60 years	1.85	1.06–3.24	0.02
Performance status			
>2 vs. ≤2	1.93	1.12–3.33	0.01

Note: In bold, statistically significant p value.

Abbreviations: CI, confidence interval; HR, hazard ratio.

improvement in the treatment modality. On the other hand, in a Danish study, it was shown that the 12-month survival of patients with MSCC secondary to LC showed a statistically significant increase between 2005 and 2010, from 4% to 19% (Morgen et al., 2013). Importantly, the small but not significant improvement in survival between the periods of diagnosis of MSCC, in this study, may be due to low incorporation of new diagnostic technologies and new therapeutic options for patients with advanced LC. A Brazilian study showed that only 9.8% of lung cancer patients received bisphosphonates and 7.4% received EGFR inhibitors (Da Silva et al., 2016, 2019). Immunotherapy was not available at our institution during the study period. An American study in which MSCC patients were treated using palliative radiotherapy and anti-PD-1 agents showed a median survival of 196 days (Farrad et al., 2019), greater than the 2.5 months described in the present study.

This study has some limitations. Data were collected retrospectively from medical records. Incomplete information for some variables may have occurred and compromised the analysis. Due to the long period of inclusion (2008 to 2017), different radiation treatment techniques may have been used to manage MSCC. Data on treatment techniques have not been collected. On the other hand, this research investigated MSCC, which is a rare complication affecting about 4% of NSCLC patients (Da Silva et al., 2017). Despite having a limited number of patients, this study focused on a selected group with a short life expectancy in order to contribute to the elaboration of the best supportive care in NSCLC patients with MSCC.

In conclusion, this study found worse PS and higher age are independent predictors of overall survival in NSCLC patients with MSCC treated with short-course radiotherapy after adjusting the potential confounding factors (PS, age and target therapy).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

GTS, TGPC, LCST and CMB participated in the conceptualisation and method, and GTS, TGPC, MMB and CMB collected data and discussed results. MMB, AK and LCST participated in the investigation and supervision of data collections. GTS, AK and LCST performed statistical analyses. LCST was the lead supervisor of the study. All authors agreed to the submitted format of the article.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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