Original Article

Survival in patients with surgically treated spinal metastases

ABSTRACT

Background: Despite the various treatment protocols available, survival evaluation is a fundamental criterion for the definition of surgical management; there are still many inconsistencies in the literature on this topic, especially in terms of the value of surgery and its morbidity in patients with very short survival.

Objective: The objective was to analyze the association of clinical, oncological, and surgical factors in the survival of patients undergoing spinal surgery for spinal metastases (SM).

Materials and Methods: A retrospective cohort of forty patients who were surgically treated at our institution for SM between 2010 and 2018 were included in the study. We applied the prognostic scales of Tomita and Tokuhashi in each patient and evaluated the systemic status using Karnofsky Performance Scale (KPS) and Eastern Cooperative Oncology Group Performance Scale. Survival rate in months was estimated using the Kaplan–Meier curve, with death considered as primary outcome and, for the evaluation of the association between the variables, the Chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test was applied for better survival. The level of statistical significance was considered as 5% ($P \leq 0.05$).

Results: The mean survival was 8.4 months. Patients with KPS <70 had a mean survival of 6.36 months, while those with KPS >70 had a mean survival of 14.48 months ($P = 0.04$). The mean survival of patients classified as ECOG 2 was 7.05 months (95% confidence interval [CI]: 3.4–10.7), and that of patients classified as ECOG 3 and 4 was 1.24 months (95% CI: 0.8–1.59). The mean survival rate among the patients with unresectable metastases in other organs was 6.3 months (95% CI: 3.9–8.9), while the survival rate of those who did not have metastases was 13.8 months (95% CI: 10.0–17.68; $P = 0.022$).

Conclusion: Survival was associated with the preoperative functional status defined by the KPS and ECOG scales and with the presence of nonresectable visceral metastases.

Keywords: Cancer, metastases, spinal cord compression, spinal metastases, surgery

INTRODUCTION

Prognosis is one of the most important factors to be considered in therapeutic decisions on spinal metastases (SM). For this reason, several scoring systems have been proposed, such as the Tomita score and Tokuhashi index.[1-6] However, these algorithms have been criticized for not considering the presence of spinal mechanical instability (MI) or the significant effects of advances in radiotherapies, such as radiosurgery. Furthermore, these algorithms neglect the demonstrated prolonged patient survival in the context of tumors with new treatment modalities, such as renal

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cell carcinoma and melanoma after the integration of new biological therapies and immunotherapy.[5,6]

Despite the various treatment protocols available, survival evaluation is a fundamental criterion for the definition of surgical management; there are still many inconsistencies in the literature on this topic, especially in terms of the value of surgery and its morbidity in patients with very short survival.[5] Patients with a more favorable prognosis and longer expected survival may warrant more aggressive interventions than those with limited prognoses.[1,5,6] Our objective in the current study was to analyze the association of clinical, oncological, and surgical factors with the survival of patients who had undergone surgery for SM.

MATERIALS AND METHODS

The current study consists of a retrospective cohort of patients who were surgically treated at our institution for SM with symptomatic spinal cord compression (SCC) and/or MI. They were treated from January 2010 to September 2018 at our hospital, a tertiary hospital that is a reference center in neurosurgery and oncology in its region in Brazil. In all cases, the surgery was performed by the same surgeon (AFJ).

Patients who were hospitalized during the period described above and met the following criteria were included in the study population: patients treated at a tertiary hospital in Brazil with the diagnosis of SCC or MI of the spine by SM and who had undergone surgical treatment, survival >3 months estimated by the personnel of the Clinical Oncology Department, patients older than 15 years, and patients who had their postoperative follow-up at the same hospital. The exclusion criteria were as follows: patients who did not undergo surgical treatment and patients whose data were not found or were insufficient for analysis. Thirteen patients with insufficient data available and five who had hematological tumors and underwent surgery were excluded from the study. After the analysis of the exclusion criteria, the sample obtained was forty patients.

The clinical data of the patients and those related to the procedure were retrospectively reviewed from the patients' medical records. We collected data on patient demographics, clinical presentation, timing of spinal surgery relative to initiation of symptoms and diagnosis, surgical information, histological diagnosis, oncological treatment, and the date of death of the patient or last follow-up visit in the case of living patients.

Surgical treatment was performed after the diagnosis of symptomatic SCC and/or instability. Epidural decompression was performed with simple laminectomy without instrumentation or laminectomy associated with surgical instrumentation (separation surgery).

Evaluation tools

Retrospectively, we performed the analysis of medical records and reviewed all pre- and postoperative imaging studies. We applied Tomita's prognostic scale,[4] the modified Tokuhashi score,[5] the Epidural Spinal Compression Score (ECSS),[6] and the Spinal Instability Neoplastic Score (SINS) score for spine stability.[7] Patients' systemic status was based on the Karnofsky Performance Scale (KPS) and Eastern Cooperative Oncology Group Performance Scale (ECOG-PS), which have both been extensively validated in cancer patients.[8,9]

Statistical analysis

Possible prognostic factors, such as age, sex, preoperative clinical state, presence of pain as the symptom that led to treatment demand, time between the development of symptoms and the surgical procedure, number of SM, presence and number of extraspinal bone metastases, and presence and number of visceral metastases and postoperative complications, were submitted to gross and multivariate statistical analysis. Survival was defined as the time between the date of surgery and death or the last follow-up visit. For statistical analysis, we stratified the survival into <6 months, between 6 and 24 months, and longer than 24 months.

After the data were collected, the analysis of the hospitalization data and their relationships as prognostic factors in relation to the primary outcome was performed. The data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). To verify the normality of the quantitative variables, the Kolmogorov–Smirnov test and Shapiro–Wilk test were applied. In both tests, variables with values of $P > 0.05$ were considered within the normality values, and therefore, as having normal distribution. Qualitative variables were presented in absolute and relative values. For the evaluation of the association between the variables, the Chi-square test, Fisher's exact test, or Fisher–Freeman–Halton test was applied. For the comparison of nonparametric quantitative variable distributions between the two study groups, the Mann–Whitney test was used, and the Kruskal–Wallis test was used for three or more groups.

To estimate the postoperative survival rate in months, the Kaplan–Meier curve was used, with death considered as an outcome and the log-rank test used for identifying the presence of prognostic factors for better survival. In all cases, the level of statistical significance was set at 5% ($P \leq 0.05$). The study was reviewed and approved by the research ethics at our institution.

RESULTS

Preoperative characteristics

After patient selection, we included forty patients who underwent surgery for metastatic epidural spinal tumors at our hospital in the analysis. The patients' mean age at the time of surgery in this study was 54.4 years (range: 23–76 years), with a predominance of patients over 55 years (55%). In relation to sex, 23 (57%) were male.

There were broad distributions of the histological type of the primary tumor. Breast (30%), lung (10%), prostate (10%), and colon (7.5%) were the most common types in our series (>50% of the cases).

According to the Tomita prognostic score, nine (22.5%) patients had a score of 2–3 points (where the treatment strategy would be aggressive tumor resection), eight (20%) had 4–5 points (marginal or intralesional resection), nine (22.5%) had 6–7 points (palliative surgery), and 14 (35%) had 8–10 points (nonsurgical treatment). Using the Tokuhashi index, most patients (28; 70%) received scores of 0–8 (estimated survival of <6 months); nine (22.5%) patients received 9–11 points (estimated survival of 6–12 months) and, finally, two (5%) patients received 12–15 points (estimated survival of >12 months).

The functional analysis of the patients was performed using the KPS scale, and most of the patients (70%) who underwent surgical treatment had KPS scores >70 (ambulatory status). Analyzing the ECOG-PS, 24 patients were classified as ECOG 0 and 1 (ambulatory, minor restrictions), 8 (27.9%) as ECOG 2 (unable to work), and 8 (20%) as ECOG 3 or 4 (bedridden).

Analyzing the imaging studies and classifying the patients according to the ECSS score, most of the patients were classified as ECSS 3 (17 patients; 42.5%; SCC without cerebrospinal fluid [CSF] lining), 12 (30%) as ECSS 2 (SCC with CSF lining visible), 3 (7.5%) as ECSS 1, and 1 (2.5%) as ECSS 1A (minimal epidural extension without SCC). In seven patients, it was not possible to perform the ECSS classification because there was no magnetic resonance imaging T2-weighted image for the evaluation. The stability of the spine was evaluated by the SINS score, with 7 (17.5%) patients stratified at 0–6 points (mechanically stable), 21 (52.5%) with 7–12 points (potentially unstable) and, finally, 12 (30%) patients at 13–18 points (mechanically unstable).

Thirty-six patients had three or fewer metastases (90%), while four had more than three noncontinuous lesions (10%). There were exclusively epidural metastases in 24 (60%) cases, epidural lesions associated with lytic bone lesions in 13 (32.5%) patients, epidural associated with blastic bone lesion in 2 (5%) patients and, finally, mixed lesions in one (2.5%) patient.

During the oncological evaluation, 23 (57.5%) patients had solid organ metastases considered unresectable by the Clinical Oncology Department multidisciplinary evaluation (multiple organs dissemination, pelaural and peritoneal carcinomatosis, multiple lymph nodes affected, and multiple lung and hepatic lesions). Among the histological results obtained, 22 (55%) patients presented tumors considered radiosensitive. Table 1 provides the detailed preoperative characteristics.

Treatment characteristics

All the patients underwent spinal cord decompression by laminectomy, and instrumentation of the spine was performed in 22 (55%) patients. Adjunctive radiotherapy at the surgery site was performed in 40 (100%) patients, and chemotherapy was performed as adjuvant therapy in 36 (90%) patients.

Overall survival

Among the 40 patients evaluated, 31 (77.5%) had died at the time of data analysis: 16 (40.0%) patients died <6 months after surgery, 14 (35.0%) between 6 and 24 months after surgery, and 1 (2.5%) after 24 months. In our series, the median overall survival (OS) was 8.4 months [95% confidence interval (CI): 3.38–13.472; Figure 1].

Clinical data and their association with survival

Table 2 shows the relationship between the patients' preoperative characteristics and survival in months.

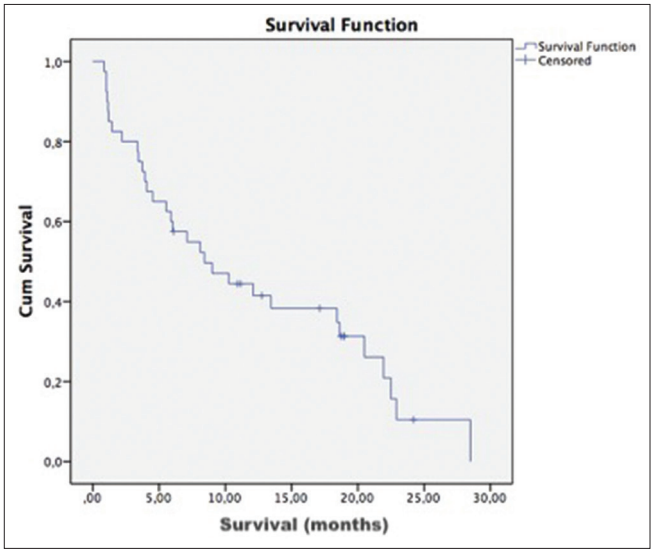

Figure 1: Kaplan–Meier curve of the general survival function

Table 1: Preoperative characteristics

	n (%)
Noncontiguous spinal metastases	
≤3	36 (90.0)
>3	4 (10.0)
Pain	
Yes	22 (55.0)
No	18 (45.0)
ECSS	
1	1 (2.5)
1A	3 (7.5)
2	12 (30)
3	17 (42.5)
Tomita	
2-3	9 (22.5)
4-5	8 (20.0)
6-7	9 (22.5)
8-10	14 (35.0)
Tokuhashi	
0-8	28 (71.8)
9-11	9 (22.5)
12-15	2 (5.0)
Extra-spinal metastasis	
0	14 (35.0)
1	7 (17.5)
2	11 (27.5)
>3	7 (17.5)
KPS	
<70	12 (30.0)
>70	28 (70.0)
Bone injury	
Epidural	24 (60.0)
Epidural + lytic	13 (32.5)
Epidural + blastic	2 (5.0)
Epidural + mixed	1 (2.5)
Radiosensitivity	
Yes	22 (55.0)
No	18 (45.0)
ECOG	
0-1	24 (60.0)
2	8 (20.0)
3-4	8 (20.0)

n - Number of cases, SINS - Spinal Instability Neoplastic Score, ECSS - Epidural spinal cord compression, KPS - Karnofsky Performance Scale, ECOG - Eastern Cooperative Oncology Group

Functional performance associated with survival

Comparing survival with the dichotomization of patients with KPS scores greater or less than 70 (ambulatory capacity), we found that, among the 12 patients with KPS <70, 8 (66.7%) died within 6 months, 3 (25%) died between 6 months and 2 years, and one patient was alive at the time of the analysis made after 4 months of the surgery.

Patients with KPS <70 had a mean survival of 6.36 months (95% CI: 1.9–10.76), whereas patients with KPS >70 had a median survival of 14.48 (95% CI: 10.78–18.17; $P = 0.04$). A KPS score <70 represented an odds ratio (OR) = 2.33 (95% CI: 1.1–4.7) of death within 6 months ($P = 0.037$). Kaplan-Meyer curve of survival related to the KPS is shown in Figure 2.

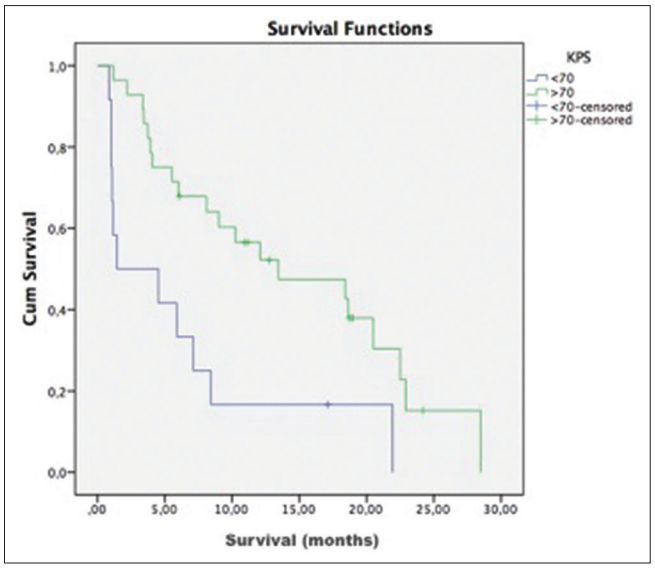

Figure 2: Kaplan–Meier curve of survival function related to the Karnofsky Performance Scale

Among the 24 patients classified as ECOG 0 and 1, 4 (16.7%) died within 6 months after surgery, 11 (45.8%) died between 6 months and 2 years, 1 (4.2%) died more than 24 months after surgery and, finally, 8 (33.3%) patients were still alive at the end of the analysis. In total, eight patients were classified as ECOG 2, and four (50%) died in <6 months. All eight patients classified as ECOG 3 and 4 died within the first 6 months. The mean survival of patients classified as ECOG 0 and 1 was 14.3 months (95% CI: 11.2–17.45). The mean survival of patients classified as ECOG 2 was 7.05 months (95% CI: 3.4–10.7), while that of patients classified as ECOG 3 and 4 was 1.24 months (95% CI: 0.8–1.59). The Kaplan–Meyer survival curve for ECOG is shown in Figure 3 ($P = 0.001$).

Status of systemic disease: Unresectable visceral metastases and survival

The presence of metastases in solid organs considered unresectable by multidisciplinary evaluation was found in 19 (47.5%) patients, of which, 11 (57.8%) died in <6 months and 7 (36.8%) died between 6 months and 2 years after surgery. One patient remained alive until the end of the analysis. The median survival among the patients with unresectable metastases was 6.3 months (95% CI: 3.9–8.9), compared with 13.8 months (95% CI: 10.0–17.68; $P = 0.022$) in those who did not have such metastases. The presence of unresectable visceral metastases presents an OR = 2.34 (95% CI: 1.33–4.13) for death in 12 months ($P = 0.01$) as shown in Figure 4.

Table 2: Comparison between the epidemiological characteristics of the surgical patients and survival time

	<6 months (*n*=16)	6-24 months (*n*=14)	>24 months (*n*=1)	Living (*n*=9)	*P*
Age (years)					
<55	9 (56.2)	8 (57.1)	0 (0.0)	1 (11.1)	0.028*
>55	7 (43.8)	6 (42.0)	1 (100.0)	8 (88.9)	
Tomita					
2-3	2 (12.5)	3 (21.4)	1 (100.0)	3 (33.3)	0.527**
4-5	5 (31.2)	3 (21.4)	0 (0.0)	0 (0.0)	
6-7	3 (18.8)	3 (21.4)	0 (0.0)	3 (33.3)	
8-10	6 (37.5)	5 (35.7)	0 (0.0)	3 (33.3)	
Tokuhashi					
0-8	11 (68.8)	11 (84.6)	0 (0.0)	6 (66.7)	0.496**
9-11	4 (25.0)	2 (15.4)	1 (100.0)	2 (22.2)	
12-15	1 (6.2)	0 (0.0)	0 (0.0)	1 (11.1)	
SINS					
0-6	3 (18.8)	4 (28.6)	0 (0.0)	0 (0.0)	0.543**
7-12	9 (56.2)	5 (35.7)	1 (100.0)	6 (66.7)	
13-18	4 (25.0)	5 (35.7)	0 (0.0)	3 (33.3)	
ECSS					
1	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0.119**
1A	1 (7.7)	0 (0.0)	0 (0.0)	2 (25.0)	
2	4 (30.8)	3 (27.3)	0 (0.0)	5 (62.5)	
3	8 (61.5)	7 (63.6)	1 (100.0)	1 (12.5)	
KPS					
<70	8 (50.0)	3 (21.4)	0 (0.0)	1 (11.1)	0.04*
>70	8 (50.0)	11 (78.6)	1 (100.0)	8 (88.9)	
ECOG					
0-1	4 (25.0)	11 (78.6)	1 (100.0)	8 (88.9)	0.001**
2	4 (25.0)	3 (21.4)	0 (0.0)	1 (11.1)	
3-4	8 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Unresectable visceral metastasis					
Yes	11 (68.8)	7 (50.0)	0 (0.0)	1 (11.1)	0.022**
No	5 (31.2)	7 (50.0)	1 (100.0)	8 (88.9)	
Radiosensitivity					
Yes	8 (50.0)	7 (50.0)	0 (0.0)	7 (77.8)	0.346**
No	8 (50.0)	7 (50.0)	1 (100.0)	2 (22.2)	

*Fisher's exact test, **Fisher–Freeman–Halton test. Percentage in relation to column. *n* - Number of cases, SINS - Spinal Instability Neoplastic Score, ECSS - Epidural spinal cord compression, KPS - Karnofsky Performance Scale, ECOG - Eastern Cooperative Oncology Group

Survival at 1 year

Table 3 shows the relationship between the mortality outcome at 1 year and the variables analyzed. Comparing the 1-year mortality of patients with unresectable visceral metastases, 17 (68%) patients who died in <1 year had nonresectable metastases compared with 8 (32%) patients who did not have these lesions. Among patients with survival >1 year, 13 (86.7%) had no visceral metastases considered unresectable. After the statistical analysis, an OR = 2.34 (95% CI: 1.3–4.1) was found. Regarding functional classifications, KPS showed no correlation with death at 12 months. Comparing ECOG with the outcome, 14 (93.3%) patients with ECOG 0–1 survived >12 months, whereas only 1 (6.7%) patient classified as ECOG 2 and no patient classified as ECOG 3–4 survived this long. The Tomita and Tokuhashi prognostic scores did not demonstrate statistical significance with death at 12 months as the outcome.

DISCUSSION

This study analyzed the survival and prognostic factors of patients who underwent surgery for SM. In our series, validated prognostic scores, such as Tomita and Tokuhashi scores, were not associated with survival prediction, as described by Ulmar *et al*.[9] The patient's functional status, as determined using the KPS and ECOG scores, proved to be a predictor of survival, as did the presence of metastases considered nonresectable by oncology.

The median OS of our patients was 8.4 months, similar to previous reports of medians of 6–14 months.[6,10-16] For instance, the study by Van der Linden *et al*. by the Dutch Bone Metastasis Study Group[17] reported a 7-month OS. Age, KPS, ECOG, and the presence of extraspinal metastases

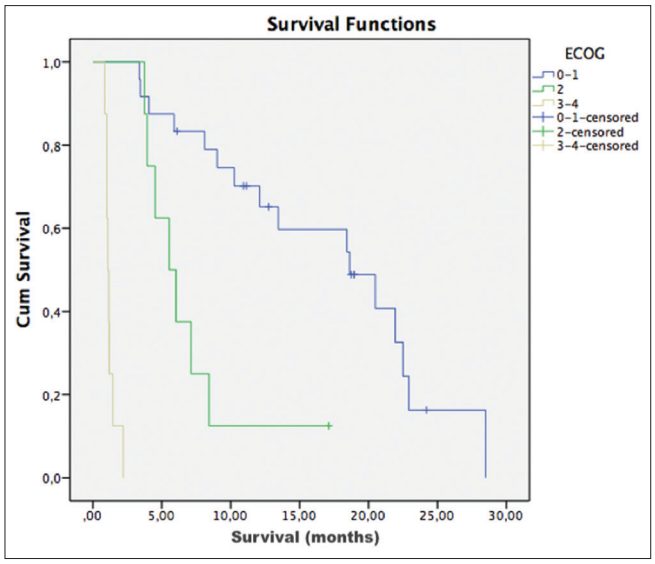

Figure 3: Kaplan–Meier curve of Eastern Cooperative Oncology Group-related survival function

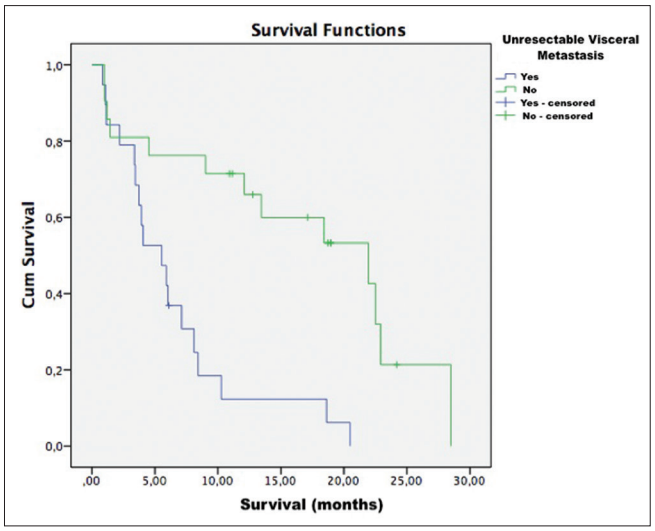

Figure 4: Kaplan–Meier curve of the survival function related to the presence of metastases considered unresectable

Table 3: Comparison between the characteristics of the patients with the death outcome at 1 year

	Dead (*n*=25)	Living (*n*=15)	*P*
Tomita			
2-3	4 (16.0%)	5 (33.3)	0.485**
4-5	6 (24.0)	2 (13.3)	
6-7	5 (20.0)	3 (26.7)	
8-10	10 (40.0)	3 (26.7)	
Tokuhashi			
0-8	18 (72.0)	10 (71.4)	0.847**
9-11	6 (24.0)	3 (21.4)	
12-15	1 (4.0)	1 (7.1)	
KPS			
>70	15 (60.0)	13 (86.7)	0.078*
<70	10 (40.0)	2 (13.3)	
ECOG			
0-1	10 (40.0)	14 (93.3)	0.003**
2	7 (28.0)	1 (6.7)	
3-4	8 (32.0)	0 (0.0)	
Nonresectable visceral metastases			
Yes	17 (68.0)	2 (13.3)	0.001*
No	8 (32.0)	13 (86.3)	

*Fisher's exact test, **Fisher–Freeman–Halton test. Percentage in relation to column. *n* - Number of cases, KPS - Karnofsky Performance Scale, ECOG - Eastern Cooperative Oncology Group

considered unresectable were characteristics associated with survival in our cohort. The functional scales of KPS and ECOG corroborated what Helweg-Larsen and Sorensen[18] observed in 153 patients with MESCC, namely, that survival was significantly greater in patients who could ambulate before and after surgery. In our series, patients with KPS >70 and ECOG 0–1, who had self-care and ambulatory capacity, presented a statistically higher survival curve than patients with worse initial evaluations did. Patients with KPS >70 had a median survival of 14.48 months (95% CI: 10.78–18.17), whereas patients with KPS <70 had a mean survival of 6.36 months (95% CI: 1.9–10.76; $P = 0.037$). The mean survival of patients with ECOG 0 and 1 was 14.3 months (95% CI: 11.2–17.45), whereas it was 7.05 months (95% CI: 3.4–10.7) in patients with ECOG 2 and 1.24 months (95% CI: 0.8–1.59) in patients classified as ECOG 3 and 4 ($P = 0.001$). Patients with ambulatory capacity are less susceptible to infection, embolic phenomena, and other complications that result in the death of bedridden patients.[2] The presence of unresectable metastases denotes advanced systemic disease in which even adjuvant palliative oncological control is more difficult. Our work identified an important correlation between the presence of unresectable metastases and the prognosis. The mean survival of patients with unresectable metastases was 6.3 months (95% CI: 3.7–8.9), which was significantly lower compared with those without metastases that were considered unresectable, which was 13.8 months (95% CI: 10.0–17.8; $P = 0.002$). The results were similar to those of Goodwin *et al*.,[19] who retrospectively analyzed 26 patients with MECV for metastatic lung carcinoma, where the outcome was survival at 3 months, and patients with visceral metastases considered nonsurgically treatable had a survival >3 months in 7% of cases compared with 50% of cases in which the patients did not present these lesions ($P = 0.0261$).

Analyzing prognostic factors related to the survival of these patients in 12 months, the variables with significance were functional classification by ECOG, in which 93.3% of the patients classified as ECOG 0–1 had a survival >1 year. In the presence of nonresectable metastases, only 10.5% of the patients had survival longer than 1 year, compared with 61.9% of patients

without these metastases. Another finding is that the presence of visceral metastasis represents an OR = 2.31 (95% CI: 1.33–4.13) at 1 year ($P = 0.01$), denoting that disseminated disease has a major effect on the survival of these patients. ECOG is a prognostic factor that has been well described in the oncological literature, as in the work of Zhang and Gong,[20] who analyzed 168 patients with metastatic lung tumor between 2014 and 2015 and reported that the 47 patients with ECOG 0–1 had a mean survival of 17.57 months (95% CI: 15.4–19.71 months), while those with ECOG 2–4 lived on 13.38 months (95% CI: 12–14.7 months) on an average.

Our study is limited by its retrospective nature, resulting in greater difficulty in applying the scores, as well as by excluding patients who submitted to nonsurgical treatment. In addition, all the cases were operated on or indicated by the same surgeon, which may constitute an inclusion bias. These limitations should be considered in the analysis of the results.

CONCLUSION

The survival of the SM patients was associated with the preoperative functional state of the patient; this was defined by the classification on the KPS and ECOG-PS scales and the presence of nonresectable visceral metastases. There was no correlation of survival with any other variable studied in our series.

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Conflicts of interest
There are no conflicts of interest.

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