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The Impact of Lung Carcinoma Histology on the Frequency of Bone Metastases*

O impacto da histologia do carcinoma pulmonar na frequência das metástases ósseas

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Abstract

Objective Lung cancer is the leading cause of death by cancer, and the bones are one of the most common sites of metastasis from this condition. This study aimed to evaluate the influence of lung carcinoma histology on the frequency of bone metastases.

Methods This retrospective study evaluated the medical records of 407 patients diagnosed with lung cancer between 2003 and 2012. The prevalence of bone metastases and their association with histological subtypes were evaluated using chi-squared tests, odds ratios (ORs) and 95% confidence intervals (CIs). The overall survival was evaluated using the Kaplan-Meier method.

Results The prevalence of bone metastases was 28.2% ($n = 115$), and the spine was the most frequently affected site (98 metastases; 32.1%). Adenocarcinoma was the most common histological subtype of lung carcinoma (46.7%), and it was significantly more frequent among patients with bone metastases (58.3% versus 42.1%; $p = 0.003$; OR = 1.92; 95% CI: 1.29–2.97). Squamous cell carcinoma was significantly less frequent among patients with bone metastases (13.0% versus 29.8%; $p = 0.0004$; OR = 0.35; 95% CI: 0.19–0.64). The median survival time after the first bone metastasis diagnosis was 4 months.

Conclusion Adenocarcinoma was the most common histological subtype of lung carcinoma, and it was significantly associated with a higher risk of developing bone metastases.

Keywords
- lung neoplasms
- neoplasm metastasis
- histology

Resumo

Objetivo O câncer de pulmão é a principal causa de morte por neoplasia, e os ossos são os principais locais de metástases desse tipo de câncer. O objetivo deste estudo foi avaliar a influência do tipo histológico do carcinoma de pulmão na frequência das metástases ósseas.

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Métodos Foram avaliados retrospectivamente os registros médicos de 407 pacientes diagnosticados com câncer de pulmão entre 2003 e 2012. A prevalência de metástases ósseas e suas associações com os subtipos histológicos foram avaliadas com o teste qui-quadrado, razões de probabilidade (RP) e intervalos de confiança (IC) de 95%. A sobrevida global foi avaliada com o método de Kaplan-Meier.

Resultados A prevalência das metástases ósseas foi de 28,2% ($n = 115$), e a coluna vertebral foi o local mais frequente (98 metástases: 32,1%). O adenocarcinoma foi o subtipo histológico mais comum de carcinoma pulmonar (46,7%) e foi significativamente mais frequente entre os pacientes com metástases ósseas (13,0% versus 29,8%; $p = 0,0004$; OR = 0,35; 95% IC: 0,19–0,64). O tempo médio de sobrevida após o diagnóstico da primeira metástase óssea foi de 4 meses.

Conclusão O adenocarcinoma foi o subtipo histológico mais comum de carcinoma pulmonar e foi significativamente associado a um maior risco de desenvolvimento de metástases ósseas.

Palavras-chave
- neoplasias pulmonares
- metástase neoplásica
- histologia

Introduction

Lung cancer is one of the three most prevalent malignancies and the leading cause of death by cancer.[1] The natural history of the disease includes aggressive evolution and reduced survival.[2,3] In addition, metastatic carcinoma is the most common malignant bone tumor, occurring in approximately 15–40% of patients with lung cancer.[4] Necropsy data show that the prevalence of bone metastases reaches 85% when the primary site is the lung.[5] In such context, bones are among the most frequent sites of metastatic lung cancer, resulting in high morbidity and reduced quality of life for these patients.[6–8]

Approximately 40% of patients with non-small cell lung cancer (NSCLC) develop bone metastases, and adenocarcinoma is the most frequent histological subtype.[4,9–13] In a previous study, we showed that lung cancer histology influences the clinicopathological features of bone metastases.[14] However, this study aimed to assess whether the risk of bone metastases development is related to the histological subtype of lung carcinoma. These findings may be useful in guiding early surveillance for bone metastases detection or interventions in high-risk groups to improve quality of life and patient survival.

Material and Methods

Population

This study retrospectively evaluated the medical records of 413 patients diagnosed with primary malignant lung tumors at our institution between 2003 and 2012. The study design was approved by our Research Ethics Committee. The inclusion criteria were histopathological diagnoses of NSCLC or small cell lung cancer (SCLC) with complete tumor staging data. Lung carcinoma was classified according to the histological subtype per the World Health Organization criteria: adenocarcinoma, squamous cell carcinoma (SCC), large cell carcinoma (LCC), unspecified NSCLC (NSCLC, unsp) and SCLC.[15]

The events of interest were occurrence of bone metastases and death. Bone metastases were diagnosed by histopathological examination of bone biopsy samples or bone scintigraphy with Tc99 plus two additional imaging tests (radiography, computed tomography or magnetic resonance imaging). These metastases were classified according to the time of diagnosis of the first bone metastasis in relation to the time of lung carcinoma diagnosis. Synchronous metastases were defined as bone metastases present at the time of lung carcinoma diagnosis, while metachronous metastases were defined as bone metastases occurring after the diagnosis of the primary tumor. To accurately assess overall survival, patients diagnosed with a second primary malignant tumor and those with unknown death dates were excluded. The minimum follow-up period was 24 months for patients who developed bone metastases (including cases of death in less than 24 months).

Statistical Analysis

The chi-square test was used to compare the proportions of histological subtypes among patients who developed bone metastases or not. The relationship between histological subtype and bone metastases occurrence was also evaluated by odds ratio (OR) and 95% confidence interval (95% CI) determinations. Overall survival was assessed using the Kaplan-Meier method. All analyzes were performed in the SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA), and a p value < 0.05 was considered statistically significant.

Results

Patients Characteristics

In total, 407 patients met the inclusion criteria and were eligible for analysis. The cohort diagram is shown

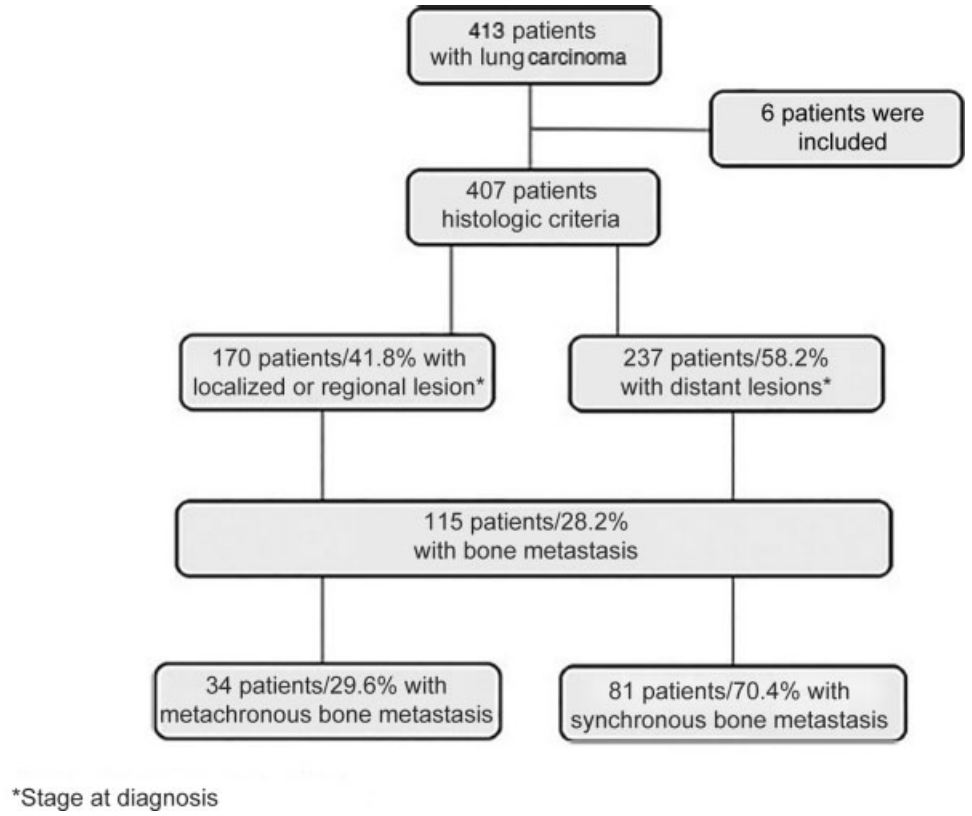

Fig. 1 Cohort diagram. Patients with pulmonary carcinoma according to the stage at diagnosis and the presence of metastasis at diagnosis or during the follow-up period.

in ►**Figure 1**, and the demographic characteristics of the patients are shown in ►**Table 1**. Average age was 63.4 years-old, and 61.4% of the patients were men. Approximately 13.5% of the patients never smoked; smokers were characterized per a smoking load of < 40 packs/year (23.6%) or ≥ 40 packs/year (62.9%). Adenocarcinoma was the most common subtype ($n =$ 190, 46.7%), followed by SCC ($n = 102$, 25.1%), NSCLC, unsp ($n = 56$, 13.7%), SCLC ($n = 48$, 11.8%), and LCC ($n = 11$, 2.7%) (►**Table 1**); A total of 115 patients presented bone metastases, and the characteristics of patients with ($n = 115$) or without bone metastases ($n = 292$) are shown in ►**Table 1**.

Bone Metastasis Prevalence

The overall prevalence of bone metastases was 28.2% ($n =$ 115). The prevalence of bone metastases according to histology is shown in ►**Figure 2**. Bone metastases were more prevalent among patients with adenocarcinoma ($n = 67$; 35.3%). Bone involvement was also observed in patients with SCC ($n = 15$, 14.7%), LCC ($n = 2$, 18.1%), NSCLC, unsp ($n = 16$, 28.6%), and SCLC ($n = 15$, 31.2%). Synchronous metastases were significantly more frequent than metachronous metastases ($n = 81$, 70.4% versus $n = 34$, 29.6%, $p =$ 0.0021).

Metastasis Number and Location

Among the 115 patients with bone metastases, there were 305 tumors (approximately 2.65 per patient). The most frequent sites were the spine (98 metastases, 32.1%), the pelvic girdle (53 metastases, 17.4%), the proximal femur and humerus (52 metastases, 17.1%), and the thoracic wall (46 metastases; 15.1%) (►**Fig. 3**).

Bone Metastasis Risk

The analysis of the proportions of patients who developed bone metastases or not according to histology showed that adenocarcinoma was the most frequent histological subtype in both groups, although the frequency of adenocarcinoma was significantly higher among patients with metastases ($n = 67$; 58.3%) compared to patients without bone metastases ($n = 123$; 42.1%) ($p = 0.003$). The frequency of SCC was significantly lower among patients who developed bone metastases ($n = 15$, 13.0% versus $n = 87$, 29.8%, p = 0.0004). However, there was no statistical difference between the other histological subgroups: LCC ($n = 2$, 1.7% versus $n = 9$, 3.1%, $p = 0.451$), NSCLC, unsp ($n = 16$, 13.9% versus $n = 40$, 13.7, $p = 0.954$), and SCLC ($n = 15$, 13.0% versus $n = 33$, 11.3%, $p = 0.623$) (►**Fig. 4**).

The associations between histology and bone metastases occurrence were evaluated through ORs and 95% CI. The ORs for bone metastases development were 1.92 (95% CI 1.29–2.97) for adenocarcinoma, 0.35 (95% CI 0.19-0.64) for SCC, 0.55 (95% CI 0.12–2.61) for LCC, 1.01 (95% CI 0.54–1.90) for NSCLC, and 1.17 (95% CI 0.61–2.26) for SCLC (►**Table 2**).

Survival

The survival results were calculated after the exclusion of 20 patients diagnosed with a second primary malignant tumor

Table 1 General characteristics of patients with lung carcinoma and according to the presence of metastasis

Characteristic	Patients with lung carcinoma		Patients with lung carcinoma		Patients with lung carcinoma	
	General cohort		Without bone metastasis		With bone metastasis	
	n = 407		n = 292		n = 115	
	n	%	n	%	n	%
Average age (range)	63.4 years-old (32–87)		65.7 years-old (42–84)		62.6 years-old (32–87)	
Gender						
Male	250	61.4	175	59.3	75	65.2
Female	157	38.6	117	40.7	40	34.8
Smoking						
Never smoke	55	13.5	30	10.3	25	21.7
$<$ 40 packs/year	96	23.6	63	21.6	33	28.7
$\geq$ 40 packs/year	256	62.9	199	68.1	57	49.6
Histology						
Adenocarcinoma	190	46.7	123	42.1	67	58.3
Squamous cell carcinoma	102	25.1	87	29.8	15	13
Large cell lung cancer	11	2.7	9	3.1	2	1.8
Non-small cell lung cancer, unspecified	56	13.7	40	13.7	16	13.9
Small cell lung cancer	48	11.8	33	11.3	15	13

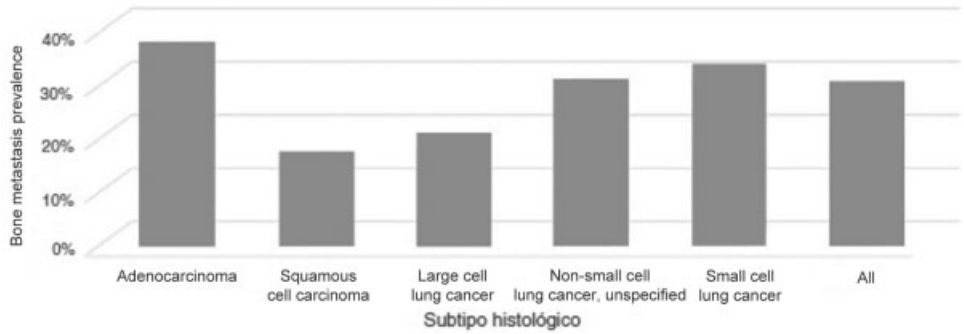

Fig. 2 Bone metastasis prevalence according to histology.

($n = 12$) and those with unknown date of death (n = 8). Median survival after bone metastases diagnosis was 4 months. Median survival for adenocarcinoma, SCC, LCC, NSCLC, and SCLC was 3.0 months, 4.5 months, 9.0 months, 2.5 months, and 4.5 months, respectively.

Discussion

In this cohort study of patients with lung carcinoma treated at the same university general hospital in Brazil, the prevalence of secondary bone involvement was approximately 28%. This result is similar to previously obtained values, demonstrating that bone tissue is one of the main sites for lung carcinoma metastasis.[16] Studies comparing the frequency of metastatic NSCLC sites showed that the frequency of bone involvement (20–40%) is comparable to that of the liver (25–30%) and the contralateral lung (40–50%).[7,10,17] We believe that assessment methods influence the incidence of bone metastases, since studies from the 1990s using bone scintigraphy demonstrated that the incidence was $<$ 20%.[18–21] On the other hand, more recent studies using positron emission tomography revealed a frequency ranging from 20 to 40%.[9,22,23] Tsuyia et al[10] identified 70 (30.4%) patients with bone metastases from lung cancer using scintigraphy, radiography, and magnetic resonance imaging. Their methods of detection and the frequency of metastases were similar to those from this study. However, our sample is larger due to the inclusion of a patient with SCLC.

The incidence of adenocarcinoma increased over time and surpassed SCC as the most prevalent lung neoplasm subtype.[24]

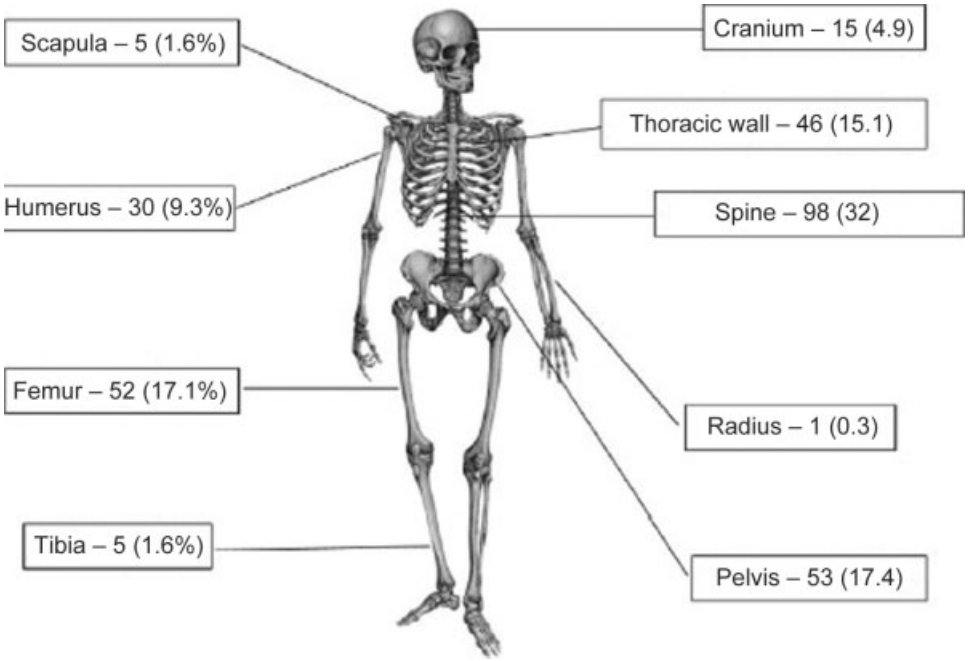

Fig. 3 Bone metastasis number and location.

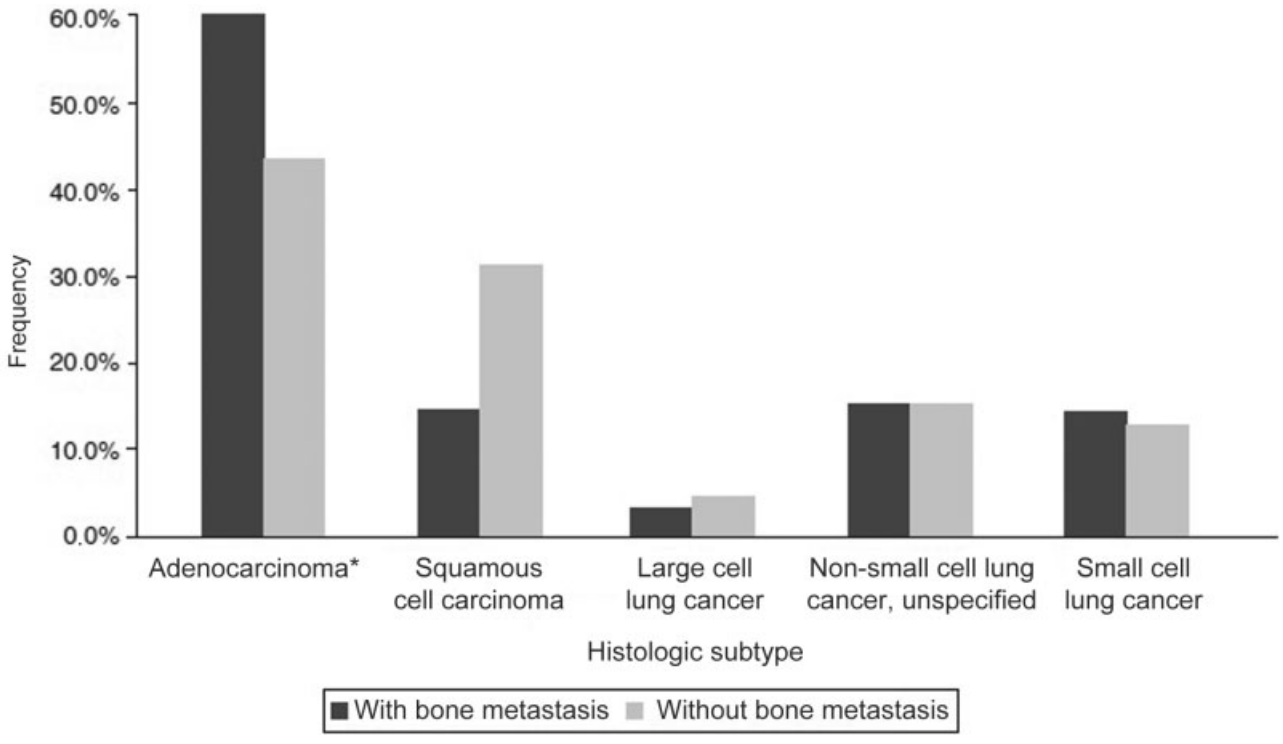

Fig. 4 Comparison of histological subtypes frequency in groups of patients with lung carcinoma that developed bone metastasis or not. *p-value < 0.05.

In this study, adenocarcinoma was the most prevalent histologic subtype among patients with or without bone metastases. Our results agree with international epidemiological reports demonstrating that adenocarcinoma accounts for $> 45\%$ of all cases.[25] However, studies in the Brazilian population have shown that SCC remains the most prevalent subtype in some areas of the country.[26] We found that the prevalence of bone metastases varied according to histology, with a higher prevalence for adenocarcinoma (35.3%; $n = 67$) and SCLC (31.2%; $n = 15$), and a lower prevalence for SCC (14.7%; $n = 15$). These results indicate that the probability of bone dissemination may vary according to the histology of lung tumor. Thus, we compared the frequencies of histological subtypes between patients with and without bone metastases to test this hypothesis. In such analysis, the frequency of bone metastases was significantly and positively associated with adenocarcinoma

Table 2 Bone metastasis risk according to lung cancer histology

Histology	Odds ratio	95% confidence interval
Adenocarcinoma	1.92	1.29–2.97
Squamous cell carcinoma	0.35	0.19–0.64
Large cell lung cancer	0.55	0.12–2.61
Non-small cell lung cancer, unspecified	1.01	0.54–1.90
Small cell lung cancer	1.17	0.61–2.26

(58.3% versus 42.1%, $p = 0.003$), and it was significantly and negatively associated with SCC (29.8% versus 13.0%, $p = 0.0004$). A recent cohort study assessed the entire Danish population and reported a higher frequency of adenocarcinoma among patients with bone metastases (50.3%) compared to all patients with lung neoplasms (37.9%), and a lower frequency of SCC (13.0%) compared to all patients with lung neoplasms (24.6%).[11] However, such study did not evaluate the possible association between histology and frequency of metastases. Lorusso et al[12] also reported that adenocarcinoma was the most frequent histological subtype, affecting 78% of the patients in their sample. Similarly, Kagohashi et al[13] reported that 67% of 24 patients with bone metastases had the adenocarcinoma subtype. In addition, in the initial study sample from Tsuya et al,[10] adenocarcinoma was observed in 61% of 259 patients with NSCLC, although the frequency among the 70 patients who developed bone metastases was not assessed. Prior to our publication of an earlier study suggesting that the histological subtype of lung carcinoma could influence the clinicopathological characteristics of bone metastases, we had found only one paper suggesting that adenocarcinoma has a particular tropism for bone dissemination, and that study reported that 45% of adenocarcinomas resulted in bone metastases.[21] The prevalence of bone metastases in the current study was a little lower (35%), although we have observed significantly higher and lower risks of bone metastases development from adenocarcinomas and SCCs, respectively.

Many studies have evaluated bone involvement in lung neoplasms without including SCLC patients, which was the second most frequent cancer subtype in the current study. Thus, it remains unclear whether the frequency and other characteristics of bone metastases for this histologic subtype differ from those of other subtypes. However, the relatively high frequency of bone metastases is consistent with the more aggressive nature of this cancer.[27] Populational-based studies from Cetin et al[11] and Sathiakumar et al[28] reported higher rates of bone dissemination for NSCLC. Nevertheless, these publications were among the few that evaluated SCLC, diagnosed in 16.7% and 13% of patients with bone metastases, respectively, secondary to lung carcinoma. These incidences are similar to the 13% we observed in this study. On the other hand, the 31.2% prevalence of bone metastases in the SCLC patients in our study was higher when compared to the prevalence of 5.8% observed by Cetin et al[11] and 23.3% noted by Sathiakumar et al.[28] These results indicate the need for further studies carefully evaluating the characteristics of bone metastases in these individuals.

In this study, most patients with bone metastases exhibited bone involvement at the time of the diagnosis of the lung neoplasm (70.4%). These results may indicate the spreading ability of lung neoplasm in the early stages of the disease.[29] However, our frequency might also have been overestimated as a result of a possible selection bias, since our institution became a reference for patients with bone tumors in 2010, resulting in a significant increase in the number of individuals with bone metastases from primary sites not determined at their hospital of origin.

The present study revealed that survival after bone metastases diagnosis is reduced, and some other studies have determined that the presence of bone metastases indicates a poor prognosis for lung cancer.[25,27,30] Hansen et al[30] published a report about the effect of bone metastases on survival in several types of carcinomas and showed that patients with lung cancer had an average survival time of 3 months after the diagnosis of these metastases. The median survival time in the current study, of 4 months, was lower when compared to that of most previous international studies and may be the result from the relatively high frequency of patients initially diagnosed in stage IV.

Our results are closer to those from a retrospective French study, which estimated a mean survival time of 5.8 months. However, the design of our study does not allow the comparison of survival after diagnosis among patients with or without bone metastases because our goal was to evaluate survival among individuals with these metastases. In addition, the primary lung site has been reported as the main prognostic factor in patients with carcinomatous bone metastases.[25,27] Thus, extreme low survival in current studies confirms three assumptions: 1) Lung neoplasia survival is low; 2) Bone metastases are a predictor of poor prognosis for any carcinoma and 3) The main prognostic factor is lung tumor location in patients with metastatic carcinomas. However, we did not observe a statistically significant difference in survival time according to histology.

The advantages of this study are the larger Brazilian population sample and the inclusion of SCLC in analyzing the association between bone metastases and lung carcinoma histology. However, our findings point to the need for further studies comparing clinicopathological features according to histology. The main limitations of this study include a possible selection bias, as the institution became a reference hospital for bone tumors in 2010 (which increased the frequency of patients with synchronous metastases).

Conclusion

Adenocarcinoma was the most common cancer subtype in patients with lung carcinoma with or without bone metastases. In addition, adenocarcinoma was associated with a higher risk of developing bone metastases, while SCC was associated with lower risk. These data suggest that patients with adenocarcinoma may benefit from a more cautious surveillance program aimed at the early detection and treatment of bone metastases.

Conflicts of Interest
The authors declare that there is no conflict of interest.

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