Bone metastasis after stage IIIA non-small cell lung cancer: risks and prognosis

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TO THE EDITOR

Lung cancer (LC) is one of the most common cancers with high morbidity and mortality rates. Stage IIIA Non-Small Cell Lung Cancer (NSCLC) is considered a heterogeneous disease due to the distinct outcomes in individuals with the same staging and the diversity of subsets in the TNM System. Approximately 54% of NSCLC with stages between II and IIIA present recurrence or metastasis.[1,2]

Bone metastases (BMs) are observed in approximately 30% of patients with advanced NSCLC. Skeletal involvement may be a source of serious complications, also known as skeletal-related events (SREs). These include pathological fractures, radiotherapy for bone pain, malignant hypercalcemia, and spinal cord compression.[3,4]

Information on the risk factors and clinical course of BMs is important to define strategies for their early detection and to predict their impact on the lives of patients with NSCLC. Therefore, the purpose of this study was to investigate risk factors for BM and survival in patients with stage IIIA NSCLC.

We conducted a retrospective cohort study including patients diagnosed with stage IIIA NSCLC between 2000 and 2014 at the Brazilian National Cancer Institute (INCA). Clinical and sociodemographic data were extracted from physical and electronic medical records. The analyzed data included age, sex, ethnicity, smoking status, performance status (PS), histology including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma subtypes; tumor size and affected regional lymph nodes; metastasis, BM, SREs, and treatments performed.

BM was confirmed by at least one of the following tests: computed tomography, magnetic resonance imaging, bone scintigraphy, pet scan, or biopsy, according to the hospital's routine. All patients were followed up for at least 60 months after the diagnosis of NSCLC, until death, or until the last visit to the hospital (loss of follow-up).

Descriptive statistics were used to analyze all variables. Survival analysis was performed using the Kaplan-Meier method. In order to calculate the risk of developing BM, univariate analysis was performed using binary logistic regression. In all analyses, p-values <0.05 were considered statistically significant. The data were analyzed using the SPSS (Statistical Package for the Social Sciences for Windows, São Paulo, Brazil) software, version 21.0.

The present study was approved by the Research Ethics Committee of the Brazilian National Cancer Institute (Protocol No. 233.245).

A total of 403 patients diagnosed with stage IIIA NSCLC were included. The patients were predominantly elderly (64.3%), male (66.3%), white (69.2%), and had a smoking history (93.3%). The majority were PS 0-1 (54.6%), had squamous cell carcinoma (49.2%), and underwent non-surgical treatment (82.9%). As for tumor size, the most frequent were T2 and T3 (36.7% and 48.4%, respectively), which exhibited dissemination to regional lymph nodes (N1=11.7% and N2=78.2%).

BM was detected in 50 patients (12.4%). The median time between the diagnosis of NSCLC and the development of BMs was 7.78 months (95% CI, 3.27 - 12.30). The most affected sites were the spine (50.0%), ribs (46.0%), and pelvis (11.0%).

The univariate analysis of the clinical and sociodemographic factors associated with the development of BM is shown in Table 1. After adjusting for potential confounding factors, the multivariate model showed a 4% reduction in the risk of developing BM, with a higher risk among younger individuals (adjusted OR 0.96, 95% CI, 0.93-0.99, p=0.023). Those with lower PS (0 and 1) at the time of NSCLC diagnosis had a 2.92-fold greater risk of developing BM (adjusted OR 2.92; 95% CI, 1.11-7.70; p=0.030).

The median survival time was 13.07 months (95% CI, 11.10-15.04) for patients who did not develop BM and 16.26 months (95% CI, 13.73-18.79) for those who did (p=0.940). After the diagnosis of BM, the median survival time was 5.84 months (95% CI, 4.39-7.30).

Among the 50 patients who developed BMs, 38.0% presented with at least one SRE. The most common SREs were radiotherapy for bone pain (22%), spinal cord compression (12%), pathological fractures (10%), and malignant hypercalcemia (8%).

After BM, the mean number of hospitalizations for patients who developed SREs was 1.63 (±1.49), and the mean number of hospitalizations for patients who did not develop SREs was 1.06 (±1.45); however, this difference was not significant (p=0.139).

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Table 1. Factors associated with the development of bone metastases (univariate analysis).

Characteristics	BM		OR (95% CI)	p-value
	Yes (N = 50)	No (N = 353)		
Age (years, mean ± SD)	59.8±9.1	64.3±10.2	0.95 (0.93-0.98)	0.004
Sex				
Women	15 (30.0)	121 (34.3)	Reference	0.550
Men	35 (70.0)	232 (65.7)	1.21 (0.63-2.31)	
Ethnicity / Skin color				
Brown / Black	10 (20.8)	109 (31.1)	Reference	0.147
White	38 (79.2)	241 (68.9)	1.71 (0.82-3.57)	
Marital Status				
Living with a partner	31 (62.0)	216 (62.1)	Reference	0.993
Living without a partner	19 (38.0)	132 (37.9)	1.00 (0.54 -1.84)	
Years of education				
≤ 8 years	33 (66.0)	257 (73.6)	Reference	0.259
> 8 years	17 (34.0)	92 (26.4)	1.43 (0.76 -2.70)	
Smoking				
No	2 (4.0)	23 (6.6)	Reference	0.490
Yes	48 (96.0)	328 (93.4)	1.68 (0.38-7.36)	
Histology				
Non-adenocarcinoma	25 (50.0)	200 (56.7)	Reference	0.376
Adenocarcinoma	25 (50.0)	153 (43.3)	1.30 (0.72-2.36)	
Tumor				
T3 and T4	28 (59.6)	206 (60.1)	Reference	0.949
T1 and T2	19 (40.4)	137 (39.9)	1.02 (0.54-1.89)	
Lymph node involvement				
N1 and N2	42 (89.4)	320 (93.8)	Reference	0.256
N0	5 (10.6)	21 (6.2)	1.81 (0.65-5.06)	
Performance Status*				
≥ 2	5 (10.0)	98 (28.1)	Reference	0.010
0-1	45 (90.0)	251 (71.9)	3.51(1.35 -9.11)	
Metastases prior to BM				
Yes	8 (16.0)	73 (20.7)	Reference	0.441
No	42 (84.0)	280 (79.3)	1.36 (0.61-3.04)	
NSCLC treatment				
Surgery	7(14.0)	62 (17.6)	Reference	0.532
Other treatments	43 (86.0)	291 (82.4)	1.30 (0.56 -3.04)	

NSCLC= Non-small cell lung cancer; BM= Bone metastasis; OR= Odds Ratio; CI= Confidence Interval. p-values in bold were statistically significant. *At the time of stage IIIA NSCLC diagnosis.

The issues addressed herein are relevant since BM has a negative impact on quality of life and promotes the increased use of healthcare resources.[4,5]

The data obtained in the present study showed that with every one year of increasing age, patients had 4% less risk of developing BM, corroborating other studies.[6] A Swedish study that addressed patients with LC showed that BM was more common in younger patients (OR 0.76, 95% CI, 0.69-0.85). The authors argue that angiogenesis may be impaired in the elderly, a fact that would compromise tumor growth and metastasis vascularization.[6]

In this study, after adjusted analysis, patients with a PS of 0 or 1 at the time of NSCLC diagnosis had a greater risk of developing BM. A recent Chinese study, which evaluated 5,051 patients with NSCLC, showed that younger patients had a higher proportion of EGFR/ALK mutations, as well as longer survival. This better prognosis can lead to more time for the development of complications of the disease, such as the development of BM.[7]

The median survival time of patients with stage IIIA NSCLC after diagnosis of BM in the current study was 5.84 months. Other studies have shown similar results.[8-10] Zhang et al. (2019) analyzed data from 125,652 patients and found a median survival rate after BM of 4 months.[8] Meanwhile, after analyzing a total of 34,584 patients, Wang et al. (2019) reported a 6-month survival rate for patients diagnosed with BM.[9]

There were some limitations in our study. Being a retrospective study with a long period of inclusion, temporal and selection bias may have been inevitable. However, this study presented advantages. The size of the analyzed population was relatively large, and patients with stage IIIA NSCLC were specifically included. Data on this group of patients are scarce in the specialized literature.

In conclusion, the present study revealed that younger patients with lower PS had a higher risk of developing BM after stage IIIA NSCLC. After BM, these patients have a poor prognosis.

AUTHOR CONTRIBUTIONS

GTS, CMB, and LMS participated in the design and planning of the study, in obtaining, analyzing, and/or interpreting data, in writing and/or critically reviewing, and in the final approval of the published version; MMZ and GJC participated in the analysis and/or interpretation of the data, as well as in the writing and/or critical review and final approval of the published version; AB and LCST participated in the writing and/or critical review and final approval of the published version.

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