Impact of Symptomatic Metastatic Spinal Cord Compression on Survival of Patients with Non-Small-Cell Lung Cancer

Gustavo Telles da Silva[1], *Anke Bergmann*[2], *Luiz Claudio Santos Thuler*[1]

OBJECTIVES: **Non-small-cell lung cancer (NSCLC) is one of the most common primary tumor sites among patients with metastatic spinal cord compression (MSCC). This disorder is related to neurologic dysfunction and can reduce the quality of life, but the association between MSCC and death is unclear. The aim of this study was to analyze the impact of the occurrence of symptomatic MSCC on overall survival of patients with NSCLC.**

METHODS: **A cohort study was carried out involving 1112 patients with NSCLC who were enrolled between 2006 and 2014 in a single cancer center. Clinical and sociodemographic data were extracted from the physical and electronic records. Survival analysis of patients with NSCLC was conducted using the Kaplan-Meier method. A log-rank test was used to assess differences between survival curves. Cox proportional hazards regression analyses were carried out to quantify the relationship between the independent variable (MSCC) and the outcome (overall survival).**

RESULTS: **During the study period, the incidence of MSCC was 4.1%. Patients who presented with MSCC were 1.43 times more likely to die than were those with no history of MSCC (hazard ratio, 1.43; 95% confidence interval [CI], 1.03–2.00; $P = 0.031$). The median survival time was 8.04 months (95% CI, 6.13–9.96) for those who presented MSCC and 11.95 months (95% CI, 10.80–13.11) for those who did not presented MSCC during the course of disease ($P = 0.002$).**

CONCLUSIONS: **MSCC is an important and independent predictor of NSCLC worse survival. This effect was not influenced by sociodemographic and clinical factors.**

INTRODUCTION

Lung cancer (LC) is the most common cancer worldwide in males and the third most common in females, accounting for almost 13% of the total cases. It is the leading cause of cancer-related death in developed countries and less economically developed countries, with an estimated 1.5 million deaths in 2012.[1] In recent years, with modern cancer therapies, the overall survival of patients with LC has improved but complications are expected to increase.[2] Non-small-cell LC (NSCLC) comprises approximately 85% of all LC cases.[3]

Many studies have found LC to be the most frequent primary tumor site among patients diagnosed with metastatic spinal cord compression (MSCC).[4-6] Morgen et al.[5] reported that LC represented 21.5% of all cases of MSCC and Phanphaisarn et al.[6] found that LC represented 41.2% of all cases of MSCC. A population-based study in patients with cancer[7] found the cumulative incidence of MSCC to be 2.5% in patients with NSCLC. MSCC is considered an oncologic emergency and without urgent treatment the spinal cord is irreversibly damaged, with permanent consequences.[8-10] Spinal involvement can cause considerable morbidity, including sensorial and motor dysfunction, severe pain, and bowel and bladder dysfunction.[9,11,12] Such neurologic complications can affect functional independence and are one of the main determinants of the quality of life in

Key words
- Cohort study
- Metastatic spinal cord compression
- Non-small-cell lung cancer
- Survival

Abbreviations and Acronyms
CI: Confidence interval
EGFR-TKI: Epidermal growth factor receptor–tyrosine kinase inhibitors
LC: Lung cancer
MSCC: Metastatic spinal cord compression
NSCLC: Non-small-cell lung cancer
PS: Performance status
RT: Radiotherapy
SD: Standard deviation

From the [1]*Research Center, National Cancer Institute and Federal University of the State of Rio de Janeiro, Rio de Janeiro; and* [2]*Research Center, National Cancer Institute, Rio de Janeiro, Brazil*

To whom correspondence should be addressed: Luiz Claudio Santos Thuler, Ph.D. [E-mail: lthuler@gmail.com]

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patients with MSCC.[10,13-15] A recent systematic review[16] and a meta-analysis[17] showed that the main therapeutic modalities used alone or in combination for MSCC treatment were radiotherapy (RT), surgery, and corticosteroids and that surgery had better therapeutic efficacy regarding life expectancy and quality of life.

Numerous studies have indicated that MSCC secondary to NSCLC is associated with poorer outcomes in patients with cancer compared with the most common human cancers such as breast and prostate.[5,18,19] There is international interest in factors associated with long-term survival after diagnosis of MSCC.[19-21] On the other hand, to our knowledge, no studies have investigated the association between the occurrence of MSCC during the clinical course of NSCLC and death. It is unclear whether the occurrence of symptomatic MSCC may affect the overall survival of patients with NSCLC. Therefore, the purpose of this study was to analyze the impact of symptomatic MSCC on the overall survival of patients with NSCLC.

METHODS

A cohort study was carried out of patients diagnosed with NSCLC between 2006 and 2014, who were treated exclusively at the Brazilian National Cancer Institute (INCA). The histologic subtypes included in this study, according to the *International Classification of Diseases for Oncology, Third Edition*, were squamous cell carcinoma (codes 8050-8076), adenocarcinoma (8140-8211, 8230-8231, 8250-8260, 8323, 8480-8490, 8550-8560, 8570-8572), and large-cell carcinoma (8012-8031, 8310).

Clinical and sociodemographic data were extracted from medical records. The variables investigated were gender, age, ethnicity, marital status, years of education ($\leq$8 or >8), history of smoking (categorized as never smokers vs. smokers/former smokers), alcohol consumption (>3 times per week, independent of the amount consumed), histology, staging, body mass index, Eastern Cooperative Oncology Group performance status (PS), history of use of epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKI), and treatment for NSCLC. The cutoff point of 60 years was used for the age variable, according to the definition of the World Health Organization, which considers the elderly as 60 years or older in developing countries. Early-stage NSCLC was considered stage I to stage IIIa and advanced stage, stages IIIb and IV. Five treatment groups were analyzed: 1) surgery; 2) chemotherapy; 3) RT; 4) surgery combined with chemotherapy; and 5) chemotherapy combined with RT.

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 the cauda equina by an extradural tumor mass.[22] The symptomatic MSCC diagnosis was confirmed by magnetic resonance imaging or spinal computed tomography.

A descriptive analysis of the variables was compiled using median $\pm$ standard deviation (SD) for continuous variables and percentage (%) for categorical variables. A χ^2 test or Fisher exact test was used to identify differences between groups.

All patients were followed from diagnosis of NSCLC until the occurrence of symptomatic MSCC, death, date of last contact (in the case of patients lost to follow-up), or the end of the study period (i.e., April 31, 2016). A Kaplan-Meier survival analysis was conducted for the exploratory evaluation of the variables associated with the time until death. To identify whether the differences between the curves were statistically significant, the log-rank test was performed. A Cox multiple regression model using the forward stepwise method was used, aiming to estimate the independent factors associated with NSCLC death that could act as confounding or effect-modifying factors in the relationship between MSCC and death. Variables with a P value < 0.05 in the univariate analysis and clinically significant variables were selected for the multiple regression model. All statistical tests were 2 tailed. Analyses were performed with SPSS (São Paulo, Brazil) version 21.0.

This research was approved by the research ethics committee of the Brazilian National Cancer Institute (INCA) (protocol CAAE: 11556513.2.0000.5274, number 233 245/2013).

RESULTS

A total of 1112 patients diagnosed with NSCLC between 2006 and 2014 were identified and included in the analysis. **Tables 1** and **2** summarize the clinical and sociodemographic characteristics of the overall study cohort and compare patients with and without MSCC. The patients were predominantly men (61.2%), white (66.5%), living with a partner (89.1%), and with a history of smoking (88.4%). Most were PS 0–1 (74.0%), more than half of the patients (63.2%) were in the advanced stage of NSCLC, 56% were classified as eutrophic, and most of the tumors were histologically classified as adenocarcinoma (52.7%). During the study period, 45 patients (4.1%) presented with symptomatic MSCC. The median age at the time of NSCLC diagnosis was 63.0 years (range, 27–89 years $\pm$9.57 SD) in patients who did not present with MSCC and 58.0 years (range, 43–82 years $\pm$8.83 SD) in patients who presented with MSCC. Compared with patients without MSCC, patients with MSCC were more likely to be younger (55.6% vs. 40.3%; $P = 0.031$), to be nonwhite (48.9% vs. 32.9%; $P = 0.021$), to have an advanced disease stage (93% vs. 61.9%; $P < 0.001$), to have adenocarcinoma (66.7% vs. 52.1%; $P = 0.020$), to have been treated with chemotherapy or RT or chemotherapy combined with RT (93% vs. 61.9%; $P < 0.001$), and to have been treated with EGFR-TKI (11.1% vs. 3.6%; $P < 0.026$). The 2 groups (patients with and without MSCC) were similar with regard to gender, marital status, schooling, smoking, alcohol intake, body mass index, and PS.

At the time of diagnosis of MSCC, 19 patients (42.3%) presented with bowel and bladder dysfunction, 17 patients (37.8%) had no motor deficit, 13 patients (28.9%) had motor deficits but were still able to walk, 8 patients (17.8%) had severe motor deficit and could not walk, and 7 patients (15.6%) presented with paraplegia. MSCC was treated using RT in 40 patients (88.8%), surgery in 4 patients (8.8%), and 2 patients did not undergo any kind of treatment (4.4%). Thirty-four patients (75.5%) received physiotherapy during hospitalization and 20 patients (44.4%) used an orthosis for pain relief and spinal stability.