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REVIEW ARTICLE

Prognostic factors in patients with metastatic spinal cord compression secondary to lung cancer: a systematic review of the literature

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Abstract
Purpose The Metastatic spinal cord compression (MSCC) secondary to lung cancer (LC) has worse prognosis when compared to MSCC related to other solid tumors. The purpose of this study is to identify the survival time and the prognostic factors in the MSCC secondary to LC.
Methods A systematic review of the literature has been carried out. Studies published between January 2005 and March 2015 were identified through the electronic database PubMed and LILACS. Two independent reviewers selected the articles.
Results 7 studies were identified, which met the inclusion criteria, involving 1010 patients. The survival in 6 and 12 months ranged between 18 and 61 %, and between 3.8 and 32 %, respectively. The median survival ranged between 2.8 and 9 months. The variables related to the survival improvement were: female, performance status 1 or 2, pre-radiotherapy and postoperative ambulatory status, absence of bone metastases and visceral metastases, interval from cancer diagnosis to spinal metastases or radiotherapy of MSCC >15 months, slower (>7 days) development of motor deficit, and the neurological status at the postoperative.
Conclusions The prognosis of the MSCC secondary to LC was poor. Considering the small number of studies identified, further research is needed to identify prognostic factors that are independent of the MSCC secondary to LC.

Keywords Metastatic spinal cord compression · Lung cancer · Prognostic factors · Systematic review

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Introduction

Lung cancer is the most common cancer diagnosed and the leading cause of cancer death in men not only in the developed countries, but also in the developing countries [1]. In Brazil, according to estimates for 2014, 16,400 new cases in men and 10,930 new cases in women are expected, representing a crude incidence rate of 1679 and 1075 per 100,000, respectively [2].

Bone metastases from lung cancer are observed in nearly 30–40 % of the patients and the skeletal involvement are often associated with significant morbidity. The most affected are the spine bones and it increases the risk of developing the metastatic spinal cord compression (MSCC), considered one of the most common and devastating complications of lung cancer, affecting in a negative way the quality of life of patients [3–5]. The treatment for MSCC has to be personalized and it includes isolated or combined use of analgesics, corticosteroids, chemotherapy, radiotherapy and surgery [6]. Even with the institution of the available therapies, the control of the evolution of the disease is bad, with a median survival time as from the moment of the diagnosis of approximately 4 months [7].

Before deciding for the most accurate treatment for patients with MSCC secondary to LC, it is important to consider the prognostic predictive factors for survival. The

personalization of the cancer treatment that has become important in the oncology field in recent years, must take into consideration the life expectancy of the patient, and it has to be particularly headed to palliative situations such as the MSCC [8]. Being aware of the prognostic factors and the survival after the MSCC in patients with lung cancer may be helpful for the determination of strategies that may cooperate, with the actions for controlling the worsening. Thus, the goal of this study is to accomplish a systematic review about the prognostic factors and survival in patients with MSCC secondary to LC.

Materials and methods

A systematic review of the literature was carried out. Indexed scientific studies were identified in the electronic database of the U.S National Library of Medicine and The National Institutes of Health (PubMed) and Latin American and Caribbean Literature in Health Sciences (LILACS), using the following keywords: lung cancer spine metastasis, lung cancer skeletal-related events, spinal cord compression lung cancer.

Complete texts in English or in Portuguese published between January 2005 and February 2015 approaching the survival and the prognostic factors of the MSCC after LC were included. Basic research articles, studies on literature review, opinion studies or letters to the editor, diagnosis studies, cost effectiveness-only studies, sensitivity analysis, studies with less than 10 patients, studies involving other types of cancer and diseases, studies that did not approach MSCC from LC separately, studies that did not included the outcome of interest, studies without abstract, duplicated studies, studies in which the series of patients was common, were excluded.

The selection of the articles was performed by two reviewers independently (G.T.S. and A.B.). Titles and abstracts were assessed to exclude those that did not meet the inclusion criteria. Full-text of the relevant articles were accessed and examined for eligibility by the two reviewers. Cases of disagreement were resolved by a third reviewer (L.C.S.T.). The references of the selected articles were analyzed in order to identify related articles that would attend the inclusion criteria.

The data in each eligible studies were independently extracted by two reviewers (G.T.S. and A.B.) using predelimited forms, which included: variables corresponding to the eligibility criteria, variables related to the participants of the study (age and gender), variables related to the characteristics of the study (design, origin of patients and the time period of the study), variables related to the type of treatment, variables related to the prognostic factors and the number of individuals included in the study.

Results

Figure 1 shows the eligibility criteria of the articles identified for this systematic review. The initial electronic research identified in Pubmed and in LILACS 802 studies that has been published about the topic; 4 additional studies were identified through a manual research in the bibliographic references of the articles.

The first review was carried out by reading the titles and the abstracts, and 722 studies were excluded. For the second stage of the review, 84 articles were fully obtained for more detailed evaluation, and 77 studies were excluded. Therefore, this systematic review contemplates the critical review of 7 studies that met the eligibility criteria for this study.

The data related to the characteristics of the study involving patients with MSCC secondary to LC are described in Table 1. Considering all the results, 1010 patients with MSCC secondary to LC were included. All the studies were based on primary data. Concerning the origin of the patients, only one study was international multicenter [9]. As for the delimitation, the studies were predominantly retrospective cohort [9–14] and 1 was prospective cohorts [15]. Regarding the histology of LC, 2 studies only analyzed patients with non-small cell lung cancer (NSCLC) [9, 10], 3 studies examined both patients with NSCLC as patients with small cell lung cancer (SCLC) [12–14] and 2 did not specify the histological type of the LC [11, 15]. There was a predominance of male patients in all studies in which this information was available, ranging from 58 to 74 % [9, 10, 13, 14]. The age was described in 5 studies [9, 10, 12–14], and it was mostly composed of elderly patients.

For the diagnosis confirmation of the MSCC, the magnetic resonance imaging was the most frequently used method [9, 10, 13–15] (Table 2). Chen et al. [10] described the circumferential compression (62 %) as the main radiographic finding, while the anterior compression (44 %) predominated in the study of Chaichana et al. [13]. The site of the lesion was described in the studies of Silva et al. [14], Chaichana et al. [13] and Chen et al. [10], preferably in the thoracic region (75.4, 67 and 61.3 %, respectively), followed by the lumbar region (21.7, 22 and 25.8 %, respectively). Other site descriptions were cervical, cervicothoracic and thoracolumbar. Chaichana et al. [13] also described as main symptoms, in order: pain (74 %), sensory alterations (67 %), motor deficit (56 %), inability to ambulate (26 %), and urinary incontinence (7 %).

Two studies assessed the functional capacity before treatment [9, 10]. For evaluating the functional recovery, Chen et al. [10] used the Frankel Scale and they observed

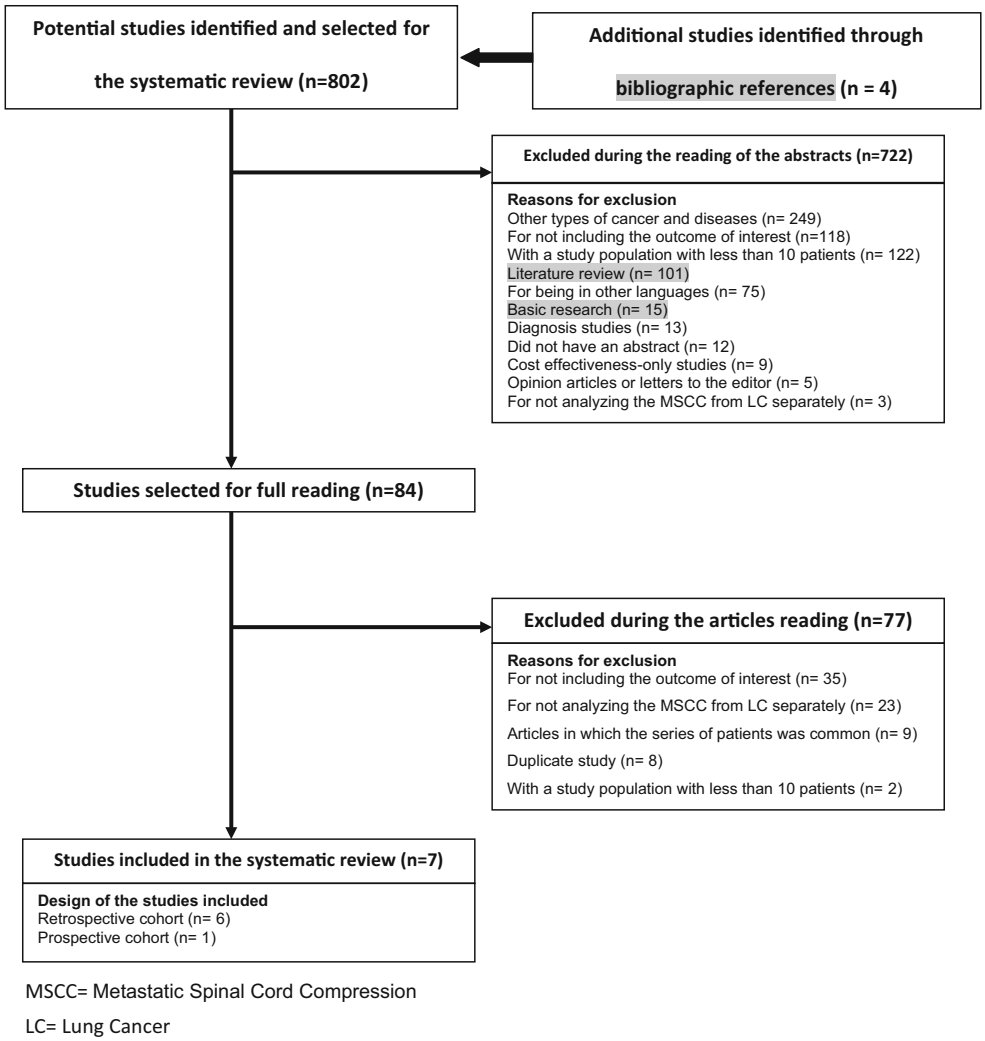

Fig. 1 Eligibility criteria of the articles identified for the systematic review. *MSCC* metastatic spinal cord compression, *LC* lung cancer

that 67 % of the patients revealed Grade C and 19 % Grade D. Yet, Rades et al. [9] observed that 63 % of the cases revealed PS 3 or 4 (data not shown).

The therapeutic modalities used were reported in 7 studies, and radiotherapy, surgery and corticosteroid were included alone, or in various combinations [9–15]. In these studies the survival in 6 and 12 months ranged between 18 and 61 %, and between 3.8 and 32 %, respectively. Yet, the median survival revealed a variation between 2.8 and 9 months. The study of Chen et al. [10] in which the treatment was surgical revealed the longest survival in 6 and 12 months. The study of Tancioni et al. [11] in which the treatment was surgery followed by radiotherapy, showed the longest median survival, 9 months (Table 2).

The prognostic factors associated with survival are shown at Table 3. In the multivariate analysis, the variables related to survival improvement were: female gender [9], performance status 1 or 2 [9, 10], pre-radiotherapy [9] and postoperative [10] ambulatory status, absence of other bone metastases and visceral, interval from cancer diagnosis to spinal metastases or radiotherapy of MSCC >15 months, slower (>7 days) development of motor deficit [9] and the neurological status at the postoperative [10].

Discussion

The interest in MSCC secondary to LC has increased for the last years and as far as we know, this is the first studies to systematically review the prognostic factors in this population.

The number of studies found in this review was small, showing the low amount of studies focused on MSCC secondary to LC. This might be explained by the fact that for a long time the studies have been limited to assess jointly MSCC caused by different types of tumors.

Table 1 Characteristics of studies involving patients with MSCC secondary to lung cancer

References	Year of publication	Study period	Design	Origin of patients	Histological type of the lung cancer	Patients with MSCC	Age
Rades et al. [9]	2012	1992–2010	Retrospective cohort	Multicenter	NSCLC = 100 %	356	<65 years old: 54 %; ≥65 years old: 46 %
Chen et al. [10]	2007	2000–2005	Retrospective cohort	Taiwan	NSCLC = 100 %	31	Median (min–max): 61,4 (20–81)
Tancioni et al. [11]	2012	2004–2007	Retrospective cohort	Italy	NS	46	NS
Ogihara et al. [12]	2006	1993–2001	Retrospective cohort	Japan	NSCLC = 90 % SCLC = 10 %	20	Median (min–max): 64,6 (35–88)*
Chaichana [13]	2009	1996–2006	Retrospective cohort	USA	NSCLC = 85 % SCLC = 15 %	27	Mean (±SD): 62 (±11)
Silva et al. [14]	2015	2007–2011	Retrospective cohort	Brazil	NSCLC = 77 % SCLC = 23 %	31	≤60 years old: 55 %; >60 years old: 45 %
Morgen et al. [15]	2013	2005–2010	Prospective cohort	Denmark	NS	499	NS

NSCLC non-small cell lung cancer, *SCLC* small cell lung cancer, *SD* standard deviation, *NS* not specified

* Age of the patients with vertebral metastases secondary to lung cancer

Table 2 Clinical aspects and survival of patients with MSCC secondary to lung cancer

References	Methods to confirm the diagnosis of MSCC	Treatment (%)	SV (%) 6 m	SV (%) 12 m	SV (%) 24 m	Median SV (months)
Rades et al. [9]	MRI AND CT	RXT = 100; SUR = 0; CC = 100	28	14	NS	NS
Chen et al. [10]	MRI, CT AND XR	RXT = –; SUR = 100; CC = NS	61	32	NS	8.8
Tancioni et al. [11]	NS	RXT = 100; SUR = 100; CC = NS	NS	16	8	9
Ogihara et al. [12]	NS	RXT = NE; SUR = 31, 57; CC = NS	27.8	11, 1	NS	NS
Chaichana et al. [13]	MRI	RXT = 56; SUR = 100; CC = 33	18	18	0	4.3
Silva et al. [14]	MRI AND CT	RXT = 90; SUR = 3; CC = NS	26.9	3.8	NS	2.8
Morgen et al. [15]	MRI	RXT = 100; SUR = 20, 98; CC = NS	NS	19* and 30**	NS	NS

MRI magnetic resonance imaging, *CT* computed tomography, *XR* X-ray, *MG* myelography, *RXT* radiotherapy, *CC* corticoids, *SUR* surgery, *SV* survival, *NS* not specified

* Survival of patients who had other kinds of treatment, except for surgery

** Survival of patients treated with surgery

However, LC has been revealed as the most common primary tumor site among patients diagnosed with MSCC (24.9 %) [16]. A similar fact occurred in the study of Morgen et al. [15], in which LC figured as the main cause of MSCC in cancer patients, representing 21.5 % of all cases. Besides that, in this study it has been observed that there is an increase in the number of LC cases over the years, with over 45 cases in 2005 and 133 cases in 2010 [15].

From the histological point of view, the SCLC tumors are distinct when compared to NSCLC. They have a more aggressive behavior, with a fast growth, early dissemination to distant sites and responsiveness to chemotherapy and radiotherapy [17]. The studies included in this

Table 3 Prognostic Factors associated with survival in the univariate and multivariate analysis

Prognostic factors	Prognostic factors for increase in survival	Studies that assessed this factor	Studies with significant results in the univariate analysis	Studies with significant results in the multivariate analysis
Age	≤64 years old	9, 10, 11	–	–
Gender	Female	9, 11	9	9
Performance Status (ECOG)	1 or 2*	9, 10, 11	9	9, 10
Number of vertebrae involved	1 or 2	9, 11	9, 11	–
Ambulatory status prior to radiotherapy	Ambulatory	9	9	9
Postoperative ambulatory status	Ambulatory	10	–	10
Other bone metastases	No**	9, 11	9, 11	9
Visceral metastases	No	9, 11	9, 11	9
Time between the cancer diagnosis and the vertebral metastases or radiotherapy	>15 months***	9, 11	9, 11	9
Time developing motor deficit	>7 days	9	9	9
Histological type of the lung cancer	Adenocarcinoma	10	–	–
Postoperative neurologic status	Improve	10	–	10
Postoperative treatment	With treatment	10	–	–
Controlled primary tumor	Yes	11	11	–
Prior therapy	Yes	11	–	–
Type of surgery	Total resection of the tumor	11	–	–
Radiotherapy schedule	Long-term	9	–	–

* In the study 10 the author considers PS 0 or 1 as a prognostic factor for survival increase

** In the study 11 the author considers few bone metastases (2–3) as a prognostic factor for survival increase

*** In the study 11 the author considers the time between the cancer diagnosis and the vertebral metastases (>12 months) as a prognostic factor for survival increase

systematic review of literature were not homogeneous regarding the histological types of LC: 2 studies considered only NSCLC [9, 10] and three other studies SCLC and NSCLC [12–14]; the remaining studies did not specify the proportion of patients with SCLC and NSCLC [11, 15]. This may have had influence on the results obtained by the authors.

This review also shows that the main therapeutic modalities used for the MSCC treatment were radiotherapy [9, 11, 13–15], surgery [10–13, 15] and corticosteroid [9, 13], used alone or in combinations. According to Mak et al. [16], the therapeutic modalities used for the management of patients with MSCC changed between 1998 and 2006, with a decrease in the use of radiotherapy, an increase in surgeries and proportional increase in the number of patients who received no treatment. However, in the study of Morgen et al. [15], the percentage of patients who underwent surgery did not increase between 2005 and 2010, ranging from 22.3 to 21.2 %.

In the study of Chen et al. [10], in which 100 % of the patients were treated with surgery, 74 % wandered after surgery and the median survival was 8.8 months. Yet, in the study of Rades et al. [9], 100 % of the patients were treated with radiotherapy and the survival in 6 and 12 months was 28 and 14 % respectively. After studying 102 cases of MSCC secondary to LC, Bach et al. [18] concluded that 95 % wandered after surgery. In this study, the median survival was 3.5 months in the group that received laminectomy followed by radiotherapy, 1.5 months in patients who received surgical treatment only and 1 month for those treated with radiotherapy only. In the non-randomized clinical trial conducted by Rades et al. [19], in which short-term radiotherapy and long-term radiotherapy were compared, the survival in 12 months was 23 % after short-term radiotherapy and 30 % after long-term radiotherapy in patients with MSCC from several types of tumors, including LC.

Many studies have demonstrated that MSCC from LC has a worse survival than what it has been observed in other types of tumors [6, 7, 20–24]. Weigel et al. [21] reported that the survival of patients with symptomatic vertebral metastases from lung cancer was 2.1 months, in patients with prostate cancer it was 7.3 months and in patients with breast cancer it was 21.2 months. Yet, in the study of Conway et al. [20] patients with MSCC from LC had a median survival of 32 days, those with breast cancer had a median survival of 74 days and those with prostate cancer 114 days. However, Morgen et al. [15] showed that

the survival of patients with MSCC secondary to LC demonstrated a statistically significant increase between 2005 and 2010, going from 4 to 19 %; in patients treated with surgery the survival increased from 9 to 30 % in the same period of time. It is important to be careful when interpreting these results, since the survival of patients with advanced LC may be increasing due to the incorporation of new therapeutic options, including treatments for specific molecular targets [17, 25].

Totally, three studies analyzed the prognostic factors in MSCC secondary to LC [9–11]. Regardless of the results being divergent for some factors, survival improvement was significantly associated with gender, performance status, number of vertebrae involved, other bone metastases, visceral metastases, ambulatory status prior to radiotherapy, postoperative ambulatory status, time between the cancer diagnosis and the vertebral metastasis or radiotherapy for MSCC, time developing motor deficit, neurological status at the postoperative, controlled primary tumor [9–11].

Two studies analyzed the female gender as an independent factor associated to survival [9, 11]. Rades et al. [9] demonstrated a significant increase in survival in female patients in the univariate and multivariate analysis. On the other hand, in the study of Tancioni et al. [11] an alteration of survival according to patients' gender was not found.

This review included three studies that assessed the association between performance status (PS) and the survival [9–11], and a better survival was observed among patients with PS 1 and 2 [9, 10].

The number of vertebrae involved, which reflects a more advanced stage of the disease, is usually associated with a poor survival [19]. The involvement of few vertebrae (1 or 2) was reported by two authors [9, 11], but a positive association with the survival was found only in the univariate analysis.

The absence of other bone metastases, absence of visceral metastases, interval from cancer diagnosis to spinal metastases or radiotherapy of MSCC were predictors for the survival in the studies that included this information in the analysis [9, 11].

In line with the results hereby exposed, studies published before this review [26, 27] show that the ambulatory status prior to radiotherapy and the interval between the diagnosis of the primary tumor and the MSCC are factors which are associated to the prognosis after the treatment of the MSCC. According to Helweg-Larsen et al. [26] primary tumors that cause MSCC with progression to inability to ambulate quickly after the cancer diagnosis are independent predictors of poor survival; the shortest time gap was recorded in patients with LC [26].

Despite few studies have focused on the analysis of prognostic factors in MSCC secondary to LC [9–11], there are several scoring systems designed to predict survival in patients with spinal metastases [28, 29]. None of them are specific for LC patients, but many parameters assessed by these scoring systems were identified in the present study such as: patient general condition, number of extraspinal bone metastases, number of spinal metastases, and presence of visceral metastases [28]. According to Tokuhashi et al. [28] the only factor included in all systems are visceral metastases and the primary site of cancer. It is important to stress that LC as the primary site of the MSCC affects negatively patient survival when compared to other cancer sites like breast, prostate or kidney [29].

In conclusion, the lack of studies focused on MSCC secondary to LC was evident. The number of patients included in the studies was small and in some studies the results were not statistically significant. Facing these results, further research is needed to identify prognostic factors that are independent predictors of MSCC secondary to LC, so that an intervention may be possible, with scientific evidence, to support the decisions about the personalized treatment of patients.

Compliance with ethical standards

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

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