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ORIGINAL ARTICLE

# Incidence and risk factors associated with the development of metastatic spinal cord compression due to bone metastasis in women with cervical cancer

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## Abstract

**Purpose** The aim of this study was to determine the incidence and factors associated with the development of metastatic spinal cord compression (MSCC) after cervical cancer (CC).

**Methods** This retrospective cohort of 3551 women with CC who underwent treatment at the Brazilian National Cancer Institute were included in the study. Clinical and sociodemographic variables were obtained from the Hospital Cancer Registry and from hospital records. A descriptive study of the population was carried out, using means and standard deviations or frequencies and percentages. The Kaplan–Meier curve was used to identify annual incidence rates. Associations between the independent variables and the outcome (MSCC) were evaluated by a univariate analysis, applying crude and adjusted odds ratios (aOR) assuming 95% confidence intervals.

**Results** The MSCC incidence was of 1.5% ($n = 51$), associated to advanced staging (aOR = 2.65, 95% CI: 1.45–4.85, $p = 0.001$) and initial treatment with concomitant chemotherapy and radiotherapy (aOR = 4.40, 95% CI: 1.74–11.13, $p = 0.002$).

**Conclusions** Our findings revealed the incidence and factors associated with MSCC, indicating a subset of patients who may be potential targets for the prevention and early treatment of this condition, indicating unprecedented and relevant data for the Brazilian epidemiological scenario due to the high CC incidence rates.

**Keywords** Metastatic spinal cord compression · Incidence · Cervical cancer · Risk factors

## Introduction

Cervical cancer (CC) is the fourth most common cancer type among women, with approximately 570,000 new cases arising each year worldwide[1]. According to Globocan, about 85% of CC cases occur in areas presenting low human development levels [1]. In Brazil, 16.35 new CC cases/100,000 women are estimated for each year of the 2020–2022 triennium, the equivalent to 16,710 cases, ranking third regarding female cancer incidence rates in the country [2]. Despite government efforts to fight the disease, mortality rates adjusted by the world population have remained high over the years, reaching 5.33/100 thousand women in 2019, comprising the fourth leading cause of cancer mortality in the country [2].

Increased patient survival is noted due to the advancement of oncological treatments, albeit with a higher incidence of bone metastases (BM) [3]. Bones comprise the third most common site of distant metastasis in CC cases, [4, 5] although BM cases in gynecological diseases are rare and scarcely reported [6]. Their incidence in CC cases ranges from 1.1 to 8.3% [7]. The incidence of pathological fracture following BM is of 57%, with the spine comprising one of its main sites, increasing the risk of Metastatic Spinal Cord Compression (MSCC) [6, 8]. Vertebral metastases cause spinal cord compression as they extend from the bone into the epidural space. These tumors involve the vertebra in 90% of

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the cases, with osteolytic lesions present in 70% of patients, often affecting the vertebral body, resulting in anterior spinal cord compression [9].

MSCC may be the initial manifestation of up to 20% of metastatic neoplasms. It affects 5–10% of all cancer patients and occurs in less than 1% of patients in CC cases [10]. It should be treated as an oncological emergency to avoid or improve neurological symptoms and maintain the patients' ability to walk and quality of life [9]. The main neurological manifestations are local or radicular pain (95%), decreased lower limb strength (60–85%), sensory disturbances (50–70%), and/or sphincter dysfunction (50–60%), causing quality of life impairments [9].

Few authors have reported the incidence and factors associated with MSCC due to BM in patients with CC so far. Knowledge of these data in Brazil is relevant because CC is a high incidence and mortality disease in the country. This knowledge can aid in the early diagnosis, monitoring and indication of appropriate MSCC treatments, providing better patient quality of life and reducing morbidity and mortality rates. The aim of this study was, therefore, to evaluate the incidence and risk factors associated with the development of MSCC due to BM after CC.

## Methods

This is a retrospective cohort study with the inclusion of patients diagnosed with CC between January 1, 2010, and December 31, 2017, identified from Hospital Cancer Registries (HCR), who underwent treatment exclusively at the Brazilian National Cancer Institute (INCA), in southeastern Brazil. Patients presenting other primary tumors at the time of CC diagnosis, or a non-epithelial CC lineage diagnosis were excluded from the study.

A total of 3397 patients were eligible. Of these, 193 were diagnosed with BM and 51 developed MSCC (Fig. 1). Cases diagnosed during the study period were followed up for at least three years from the date of cancer diagnosis or until death or loss of follow-up. The data collection instrument

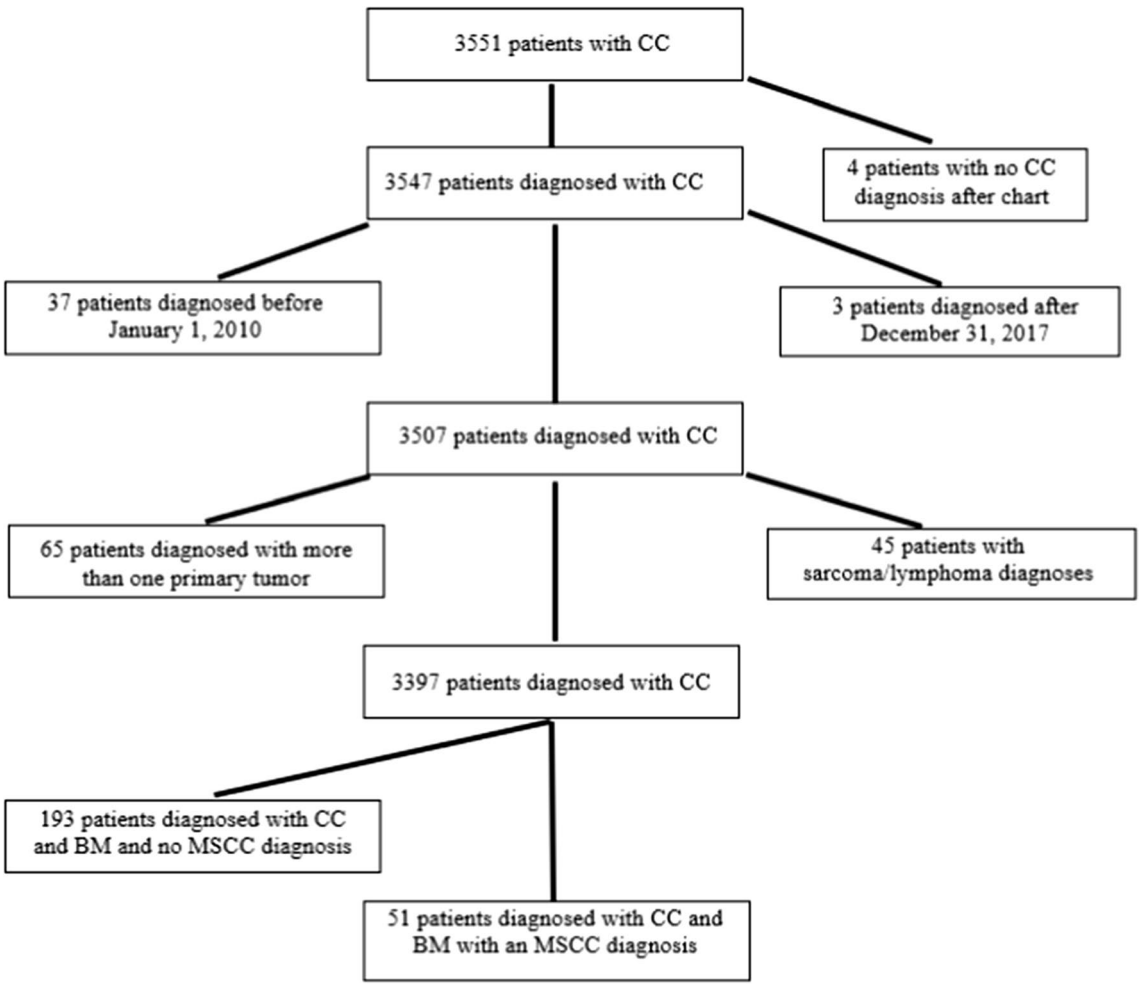


**Fig. 1** Flowchart indicating patient selection

consisted of a form comprising sociodemographic, epidemiological, clinical-pathological and follow-up variables obtained from the HCR, electronic medical records or physical hospital records. Included variables comprised race/skin color, education, age, city of origin, histology, clinical tumor staging, initial disease treatment and the presence of BM, MSCC, or other metastases. Patients with cervical cancer were staged according to the FIGO (The International Federation of Gynecology and Obstetrics) clinical staging. Based on current guidelines, surgical treatment was indicated for patients in initial stage and adjuvant treatment performed according to postoperative oncological results. On the other hand, patients with advanced staging (locally advanced disease or metastases) underwent concomitant chemotherapy and radiotherapy as the exclusive treatment.

The main outcome, MSCC, was confirmed in all cases by imaging studies (Computed Tomography and Magnetic Resonance Imaging) reviewed by an experienced radiologist.

A descriptive study of the population was carried out using central tendency measures (means and standard deviations) for the continuous variables and frequency distribution for the categorical variables. The normality of the continuous variable distributions was analyzed using the Kolmogorov Smirnov test. The cumulative incidence was calculated by dividing the number of MSCC cases by the total number of CC patients × 100. The Kaplan–Meier curve was used to calculate annual incidence rates (incidence density). Associations between the independent variables and the outcome were assessed by a logistic regression analysis, employing crude and adjusted odds ratios (OR), assuming 95% confidence intervals. To control for potential confounders, variables presenting $p < 0.15$ were selected for the multiple model using the stepwise forward method. The model's goodness of fit was determined by Hosmer and Lemeshow test values. $P$ values $< 0.05$ were considered statistically significant. Data were processed using the SPSS software, version 24.0.0.0 (2016).

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

The research must be published in accordance with internationally accepted guidelines, therefore the STROBE declaration has been completed and is attached.

## Results

### MSCC incidence

During the follow-up period, 193 women developed BM (5.7%) and 51 of them developed MSCC. The cumulative incidence of MSCC was 1.5% (95% CI: 1.1–2.0). Incidence rates were higher in the first five years of the study, but new MSCC cases were observed in up to 10 years of follow-up (Table 1, Fig. 2).

### Study population description

The study population included 3397 CC patients with a mean age at the first consultation of 48.8 years (SD ± 14.0). A total of 56.1% were non-white, 51.7% presented education ≥ 8 years and 57.6% resided in other cities in the state of Rio de Janeiro (interior). Regarding tumor characteristics, 78.2% presented cervical squamous cell carcinoma (CSCC) as the histological type and 42.7% exhibited a clinical stage III and IV, and 65.2% patients undergoing initial treatment with concomitant chemotherapy and radiotherapy as an exclusive modality (Table 2).

**Table 1** Incidence rates of MSCC due to BM in CC patients

| Period | Patients at the beginning of the period | New events during the period | Accumulated events during the period | Rate during the period | Accumulated rate during the period | Accumulated rate at the end of the period by 1000 |
|---|---|---|---|---|---|---|
| 1st year | 3396 | 15 | 15 | 0.000336 | 0.0043527 | 4.4 |
| 2nd year | 2893 | 14 | 29 | 0.000438 | 0.0098053 | 9.8 |
| 3rd year | 2108 | 8 | 37 | 0.000617 | 0.0140184 | 14.0 |
| 4th year | 1554 | 5 | 42 | 0.000875 | 0.017646 | 17.6 |
| 5th year | 1064 | 3 | 45 | 0.001001 | 0.0205342 | 20.5 |
| 6th year | 740 | 3 | 48 | 0.002058 | 0.0253575 | 25.4 |
| 7th year | 409 | 1 | 49 | 0.002381 | 0.0277384 | 27.7 |
| 8th year | 191 | 1 | 50 | 0.003636 | 0.0313748 | 31.4 |
| 9th year | 56 | 0 | 50 | 0 | 0.0313748 | 31.4 |
| 10th year | 4 | 1 | 51 | 0.005495 | 0.0368693 | 36.9 |

MSCC, Metastatic spinal cord compression; BM, Bone metastasis; CC, Cervical cancer

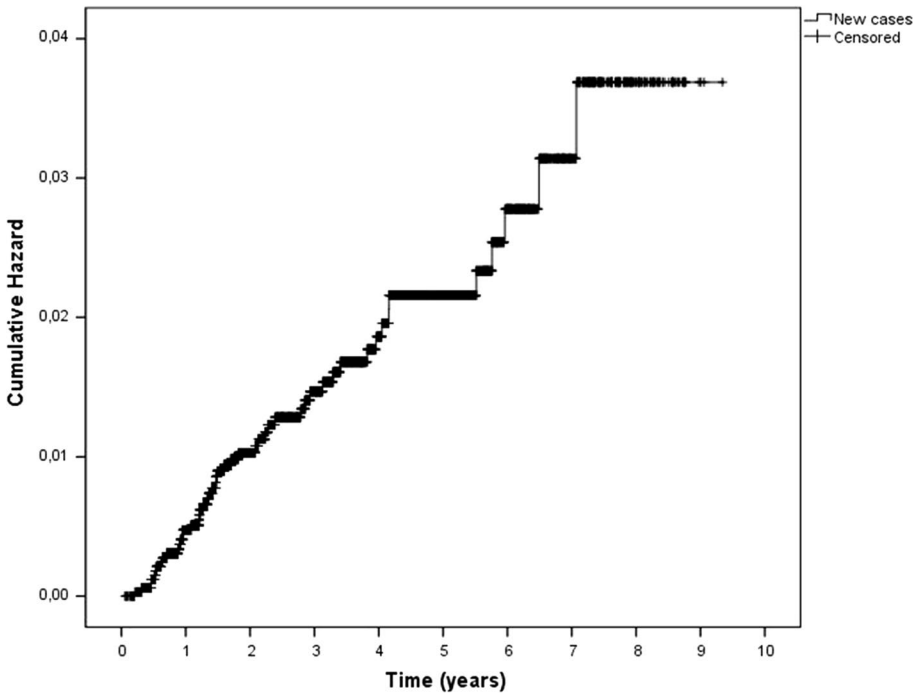


**Fig. 2** Metastatic spinal cord compression incidence rate

## Risk factors associated with the development of MSCC

Regarding the univariate analysis, a 2% risk reduction of developing MSCC was observed at every one year of life (OR = 0.98, 95% CI: 0.96–1.00, $p = 0.030$). Advanced staging (III and IV) were also associated with a higher risk of MSCC (OR = 2.81, 95% CI: 1.54–5.12, $p < 0.001$), as well as concomitant chemotherapy and radiotherapy (OR = 4.07, 95% CI: 1.73–9.56, $p = 0.001$), lung metastasis (OR = 3.27, 95% CI: 1.37–7.81, $p = 0.008$) and one or more metastases (OR = 2.25, 95% CI: 1.19–4.25, $p = 0.013$). The other analyzed variables were not statistically associated with the development of MSCC in this population (Table 2).

After the adjusted analysis, the data revealed that women presenting advanced clinical stage presented a 2.65-fold higher risk of MSCC (95% CI: 1.45–4.85, $p = 0.001$) and that patients undergoing concomitant chemotherapy and radiotherapy presented a 4.40-fold higher risk (95% CI: 1.74–11.13, p = 0.002). The Hosmer and Lemeshow test indicated a good fit of the multiple model ($p = 0.183$).

## Discussion

In the present study, carried out in a single referral cancer treatment center, the incidence of MSCC in patients with CC was of 1.5%. A lower incidence has been reported in other studies, occurring in less than 1% of patients [10, 11], perhaps due to the longer follow-up period performed herein (10 years). In a large study carried out in Canada, which investigated MSCC in 3473 cancer patients over a period of 5 years, a 0.03% incidence was observed in patients with CC [12]. In another assessment, only two MSCC cases were detected in a retrospective cohort study that analyzed neurological complications in 1219 patients with CC for 15 years [13]. In a case series report, five patients were diagnosed with MSCC among 121 women with CC, in a period of one year [14]. In another cohort study with a long follow-up period (16 years), 361 CC cases were reviewed and a 2% incidence was reported (seven cases) [15].

In the present study, advanced CC stage (III and IV) and initial treatment with concomitant chemotherapy and radiotherapy as an exclusive modality comprised independent risk factors for the development of MSCC. MSCC usually occurs in patients with advanced or metastatic disease [9, 16]. Furthermore, concomitant chemotherapy and radiotherapy as an exclusive modality were associated with an increased risk of developing bone metastasis in patients with CC [17].

The frequency of neurological complications in advanced CC stages has been reported as 8% [13]. No recent studies were observed in the CC population that reported the risk factors associated with the development of MSCC, but other studies involving patients with breast, lung and prostate cancer analyzed risk factors associated with the development of BM and skeletal related events, which include MSCC, corroborating our findings [18–21].

The number of vertebrae with BM in patients with prostate and lung cancer was shown to be significantly associated with the development of MSCC [22, 23]. A comprehensive

**Table 2** Analysis of risk factors for the development of MSCC due to BM in patients with CC

| Characteristics | *N* (%*) | MSCC | | OR (95% CI) | *p* value |
|---|---|---|---|---|---|
| | | Yes *N* (%*) | No *N* (%*) | | |
| Age, mean (± SD) | 3397 (48.8) | 44.6 (± 12.1) | 48.9 (± 14.0) | 0.98 (0.96–1.00) | 0.030 |
| *Race/Skin Color* | | | | | |
| White | 1492 (43.9) | 21 (1.4) | 1471 (98.6%) | Reference | |
| Non-white | 1905 (56.1) | 30 (1.6) | 1875 (98.4%) | 1.12 (0.64–1.97) | 0.691 |
| *Education* | | | | | |
| ≥ 8 years | 1755 (51.7) | 21 (1.2) | 1734 (98.8) | Reference | |
| < 8 years | 1637 (48.3) | 30 (1.8) | 1607 (98.2) | 1.54 (0.88–2.70) | 0.131 |
| *Municipality of origin* | | | | | |
| Rio de Janeiro | 1441 (42.4) | 20 (1.4) | 1421 (98.6) | Reference | |
| Others | 1956 (57.6) | 31 (1.6) | 1925 (98.4) | 1.14 (0.65–2.2) | 0.641 |
| *Histology* | | | | | |
| Others | 741 (21.8) | 7 (0.9) | 734 (99.1) | Reference | |
| Cervical squamous cell carcinoma | 2656 (78.2) | 44 (1.7) | 2612 (98.3) | 1.77 (0.79–3.94) | 0.164 |
| *Clinical staging* | | | | | |
| I and II | 1916 (57.3) | 16 (0.8) | 1900 (99.2) | Reference | |
| III and IV | 1428 (42.7) | 33 (2.3) | 1395 (97.7) | 2.81 (1.54–5.12) | < 0.001 |
| *Surgery* | | | | | |
| Yes | 740 (21.8) | 1 (0.1) | 739 (99.9) | Reference | |
| No | 2657 (78.2) | 50 (1.9) | 2607 (98.1) | 14.17 (1.96–107.77) | < 0.009 |
| *Chemotherapy + Radiotherapy* | | | | | |
| No | 1182 (34.8) | 6 (0.5) | 1176 (99.5) | Reference | |
| Yes | 2215 (65.2) | 45 (2.0) | 2170 (98.0) | 4.07 (1.73–9.56) | < 0.001 |
| *Lung metastasis* | | | | | |
| No | 3260 (96.0) | 45 (1.4) | 3215 (98.6) | Reference | |
| Yes | 137 (4.0) | 6 (4.4) | 131 (95.6) | 3.27 (1.37–7.81) | 0.008 |
| Liver metastasis | | | | | |
| No | 3339 (98.3) | 49 (1.5) | 3290 (98.5) | Reference | |
| Yes | 58 (1.7) | 2 (3.4) | 56 (96.6) | 2.40 (0.57–10.11) | 0.233 |
| *Total metastases* | | | | | |
| None | 2942 (86.6) | 38 (1.3) | 2904 (98.7) | Reference | |
| 1 or more | 455 (13.4) | 13 (2.9) | 442 (97.1) | 2.25 (1.19–4.25) | 0.013 |

*Percentages in rows/ MSCC, metastatic spinal cord compression; BM, Bone metastasis; CC, Cervical cancer; OR, oDds ratio; CI, Confidence Interval

systematic review sought to identify risk factors associated with MSCC in patients with breast, prostate and lung cancer, and found a significant association for the number of spinal vertebrae metastases, time between primary tumor diagnosis and BM and the type of primary tumor[18]. The presence of extraosseous metastases in the lung, liver and brain have been reported as risk factors associated with the development of BM in women with CC, which may contribute to progression to MSCC [20]. Factors that contribute to the development of BM in 91 patients with CC comprise the adenocarcinoma histological type, advanced staging and presenting other metastases at the time of BM diagnosis [17]. Another study followed 4620 CC patients, 51 of which (1.1%) developed BM. A total of 80.5% of the cases had MSCC and over than 75% presented multiple bone and extra-pelvic metastases [4].

Data from previous research involving other types of cancer pointed out age as a factor associated with the development of MSCC [12, 15, 24, 25]. In the present study, although the incidence of MSCC decreased with age in the univariate analysis, this variable lost statistical significance in the multiple analysis. On the other hand, histological type was not significantly associated with the development of MSCC, similar to the findings reported by other authors [13].

However, an MSCC diagnosis is often not established until significant neurologic deficits are present, which can make functional recovery difficult. At this stage, the treatment

presents itself as an oncological emergency, often with reduced effectiveness and high costs. Therefore, the early diagnosis of MSCC, prior to symptom development, may allow for treatment and the preservation of neurological patient function [25].

One of the limitations of the current study is related to its retrospective nature, which may have influenced the quality of information and the loss of data extracted from physical and electronic medical records. However, the study also presents positive points. The population size was large, as all patients with CC were included within the stipulated period. There was a long follow-up period and all MSCC diagnostics were reviewed by an experienced oncology radiologist. Another positive point is that, to our knowledge, this is the first study in the world on the incidence and risk factors associated with the development of MSCC in patients with CC, pointing out relevant data on this complication.

The present cohort study described the incidence and risk factors associated with the development of MSCC in patients with CC in Brazil. Our findings reveal that presenting an advanced stage of the disease and undergoing initial treatment based on concomitant chemotherapy and radiotherapy are associated with MSCC development. These results are relevant to the country's epidemiological scenario, due to the high incidence rates of CC in Brazil and indicates a subset of patients that may be potential targets for MSCC prevention and early treatment.

**Author's contribution** Study Conception and Design: AGG, LCST, GST, AB; Acquisition of Data: AGG, JBR, CLC; Supervision: LCST, GST, AB; Analysis and Interpretation of Imaging Exams: CLC, AGG; Analysis and Interpretation of Data: AGG, LCST, AB; Drafting of Manuscript: AGG, LCST, GTS; Critical Revision: All authors.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This retrospective cohort study complies with the ethical standards by Research Ethics Committee of INCA and with the Declaration of Helsinki in 1964 and its later amendments or comparable ethical standards.

**Consent to participate** The study was approved by the Research Ethics Committee of INCA—CAAE: 20921019.5.0000.5274, which, due to its characteristics, waived the use of a Free and Informed Consent Form.

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