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Original Article



# Incidence and risk factors for the development of cerebral metastasis in cervical cancer patients

**Juliana de Brito Rangel** [1,2] **Alessandra Grasso Giglio** [1,2]
**Cristiane Lemos Cardozo** [2] **Anke Bergmann** [2] **Luiz Claudio Santos Thuler** [1,2]

[1]Federal University of Rio de Janeiro State (UNIRIO), Rio de Janeiro, Brazil
[2]Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil



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**Correspondence to**
**Luiz Claudio Santos Thuler**
Instituto Nacional de Câncer - Coordenação de Pesquisa Clínica - Rua André Cavalcanti, 37/Anexo, 3o andar, Centro, Rio de Janeiro, RJ 20231-050, Brazil.
Email: lthuler@gmail.com



**ORCID iDs**
Juliana de Brito Rangel
https://orcid.org/0000-0003-3459-0435
Alessandra Grasso Giglio
https://orcid.org/0000-0002-6716-5884
Cristiane Lemos Cardozo
https://orcid.org/0000-0001-5792-1431
Anke Bergmann
https://orcid.org/0000-0002-1972-8777
Luiz Claudio Santos Thuler
https://orcid.org/0000-0003-2550-6537

**Conflict of Interest**
No potential conflict of interest relevant to this article was reported.

## ABSTRACT

**Objective:** Cerebral metastasis (CM) in cervical cancer (CC) cases, although rare, results in high lethality rates. The present study aimed to assess CM incidence in a Brazilian reference CC center and evaluate the risk factors for CM development. Retrospective observational study of patients diagnosed with CC between 2010 and 2017.
**Methods:** Cumulative CM incidence and incidence density were evaluated. Characteristics associated to CM development risks were identified using crude (cOR) or adjusted (aOR) odds ratios.
**Results:** A total of 3,397 patients were included in this study. Patient age ranged from 18 to 101 years, with a mean age of 48.8±14.0. After a mean follow-up time of 3.2±2.1 years, 51 CM cases were identified, resulting in a cumulative incidence of 1.5% (95% confidence intervals [CI]=1.12–1.97) and an incidence density at the end of the 6th year of 27.4 per 1,000 women/year. Advanced clinical stage (aOR=3.15; 95% CI=1.16–8.58; p=0.025), the presence of previous lung metastasis (aOR=4.04; 95% CI=1.82–8.94; p=0.001) and the adenocarcinoma (aOR=2.90; 95% CI=1.46–5.76; p=0.002), adenosquamous carcinoma (aOR=7.33; 95% CI=2.87–18.73; p<0.001), undifferentiated carcinoma (aOR=14.37; 95% CI=3.77–54.76; p<0.001) and neuroendocrine carcinoma (aOR=21.31; 95% CI=6.65–68.37, p<0.001) histological types were associated with a higher risk for CM development. CM risk was higher in the first years of follow-up, with no cases observed after the 6th year.
**Conclusion:** CC patients in advanced clinical stages, displaying previous lung metastasis and non-squamous histological types are at high risk of developing CM.

**Keywords:** Neoplasm Metastasis; Brain, Uterine Cervical Neoplasms; Risk Factors

### Synopsis

In total of 3,397 patients with cervical cancer were followed-up for more than 3 years (median follow-up) and 51 cerebral metastasis (CM) cases were identified (incidence at the end of the 6th year of 27.4 per 1,000 women/year). Non-squamous histology, previous lung metastasis and advanced stages at diagnosis were associated with CM.

**Author Contributions**
Conceptualization: R.J.B., T.L.C.S.; Data curation: R.J.B., G.A.G., C.C.L.; Formal analysis: R.J.B., B.A., T.L.C.S.; Supervision: B.A., T.L.C.S.; Writing - original draft: R.J.B., G.A.G., C.C.L., B.A., T.L.C.S.; Writing - review & editing: R.J.B., G.A.G., C.C.L., B.A., T.L.C.S.

## INTRODUCTION

Cervical cancer (CC) is considered a potentially preventable cancer through the human papillomavirus (HPV) vaccine and the screening of precursor lesions by colpocytology or by identifying cervix HPV. These measures are still, however, not widely accessible in developing countries, which continue to display high incidence and mortality rates from this type of cancer [1].

In Brazil, for example, the National Cancer Institute (INCA) estimated a total of 16,710 CC cases in 2021, with an incidence rate of 16.35 cases/100,000 women, comprising the third most common cancer in women [2].

In the presence of distant disease, the 5-year CC survival rate is low, of 16.5% compared to 91.5% for localized disease, and dissemination to the central nervous system (CNS) is commonly associated with death within 6 months of cerebral metastasis (CM) diagnosis [3]. CM is, thus, a marker of longevity limitation independent of tumor burden [4].

CM rates are 10 times more common than primary CNS neoplasms, frequent in lung, breast and melanoma cancers, and considered rare in CC cases, with incidences ranging from 0.4% to 2.3% in population studies [3-5]. CM comprises not only the brain parenchyma but also the leptomeninges. A recent systematic review indicates that a total of 716 CM patients and less than 30 meningeal carcinomatosis cases have been described worldwide in the English-language literature in the last 50 years [5].

Henriksen first described CM in CC cases in 1949 [6], and few incidence studies have been published since then, usually comprising retrospective and single-center assessments [7-9]. Cagney et al. [10] highlighted the main invasive solid tumors with CM at diagnosis in a North American population base in 2017 and reported a CM incidence at diagnosis in CC cases of 0.38%, also indicating that almost half of all CM cases were synchronous with bone and pulmonary metastases.

Weed et al. [11] hypothesized that cervix neuroendocrine carcinoma seems to increase CM incidence after observing three CM cases (20%) among 15 patients presenting this histological type in a study carried out at the University of Kansas between 1977 and 1997. Hwang et al. [9] reported 11 CM cases, almost all in advanced stage, and 54% presenting non-squamous CC histology. The literature review conducted by Bi and Li [12] indicates that most CM are associated with poorly differentiated histological types, non-squamous subtypes and advanced staging, and the largest and most recent meta-analysis produced on the subject to date has indicated that, although squamous histology is the most common among CC cases, unusual histological subtypes are often associated with CM [5].

Increased CM incidence reports are expected with the advancement of imaging methods and primary tumor control. Thus, it is important to understand the characteristics that may increase the risk of CM development following CC diagnosis, in order to devise screening and early treatment strategies for this frequently lethal condition. Within this context, the present study aimed to assess CM incidence in a Brazilian reference center for CC treatment and evaluate the characteristics that may be associated with increased CM development risks.

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## MATERIAL AND METHODS

### 1. Protocol and registration

A retrospective observational study comprising women with confirmed histopathological CC diagnosis between January 2010 and December 2017 attending the INCA, in Rio de Janeiro, Brazil was performed. The study was approved by the INCA Research Ethics Committee under number: 3,635,764, CAAE - 20347419.4.0000.5274.

### 2. Patients

Patients over 18 displaying invasive epithelial lineage CC were included. Clinicopathological, sociodemographic and follow-up variables were obtained from hospital records, comprising age, race/skin color, education, city of origin, histological type, clinical staging at diagnosis, origin of referral to the cancer center, alcoholic beverage and tobacco product consumption, marital status and histology. The cases were followed for at least 3 years from diagnosis in the hospital unit.

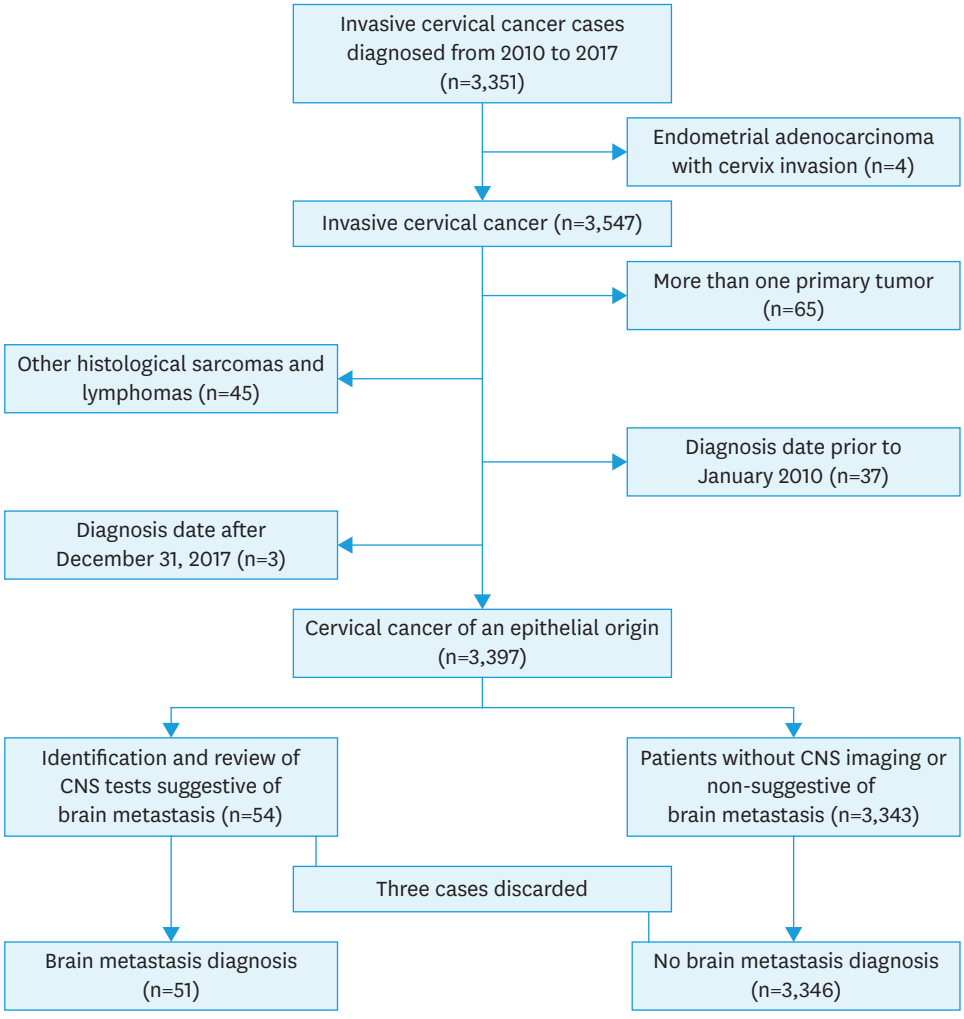


**Fig. 1.** Patient identification flow chart.
CNS, central nervous system.


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All histopathological reports for the 3,551 cases of malignant cervix neoplasms registered at the institution between 2010 and 2017 were reviewed. Four cases comprising endometrial adenocarcinoma extending to the uterine cervix, 40 cases with diagnostic confirmation performed outside the study period, 65 cases in which CC was the second primary tumor and 45 cases of other histological lineages (sarcomas and lymphomas) were excluded from the study (**Fig. 1**). After applying these exclusion criteria, a total of 3,397 patients remained in the assessment. The imaging exams (computed tomography and/or cranial magnetic resonance) of all patients with suspected CM were re-evaluated by a radiologist experienced in neuroradiology assessments. Patients with clinical suspicions but no available image exams or those presenting other radiological diagnoses were not counted as CM cases.

At INCA, during the period covered by the study, the primary CC treatment was consistent with established guidelines, not being stratified according to histology, with the exception of neuroendocrine tumors, in which all patients received chemotherapy with etoposide and cisplatin, even in early stages. Patients presenting early disease were typically treated with surgery, followed by radiation and chemotherapy when indicated, while those with advanced or metastatic disease were treated with chemotherapy with or without radiation.

### 3. Statistical analyses

A descriptive study was carried out using central tendency (mean or median) and dispersion (standard deviation or interquartile range) measures for continuous variables and frequency distributions for categorical variables. Potential associations between CM development and independent variables were assessed using Pearson's chi-square test or Fisher's exact test. Crude (cOR) and adjusted (aOR) odds ratios were calculated employing a logistic regression assuming 95% confidence intervals (CIs). Variables with p-values <0.15 in the univariate analyses were tested in a multivariate model, beginning with the variable most strongly associated to the outcome and continuing until no other variable reached the established significance level of $p<0.05$. Only variables with $p<0.05$ were maintained in the final model.

## RESULTS

A total of 3,397 patients with CC were included in this study. Mean age was of 48.8±14.0 years, most were white or brown (87.9%), lived in the interior of the state of Rio de Janeiro (57.6%) and were users of the Brazilian Unified Health System (In Portuguese: *Sistema Único de Saúde* - SUS) (83.9%). The predominant histological type was squamous cell carcinoma (78.2%), most frequently at clinical stage III (34.6%).

A total of 51 CM cases were identified during the study period. Of these, 48 comprised only CM, two comprised meningeal carcinomatosis and one CM case was associated with

**Table 1.** Incidence density of cerebral metastasis in women with cervical cancer per year of follow-up

| Period | Population at risk at the beginning of the study period | New cases during the study period | Incidence density | Incidence density per 1.000 |
|---|---|---|---|---|
| 1st year | 3,397 | 18 | 0.0057 | 5.7 |
| 2nd year | 2,898 | 12 | 0.0106 | 10.6 |
| 3rd year | 2,107 | 13 | 0.0177 | 17.7 |
| 4th year | 1,552 | 3 | 0.0199 | 20.0 |
| 5th year | 1,064 | 2 | 0.0224 | 22.4 |
| 6st year* | 739 | 3 | 0.0274 | 27.4 |

*No cerebral metastases were recorded after the 6th year.


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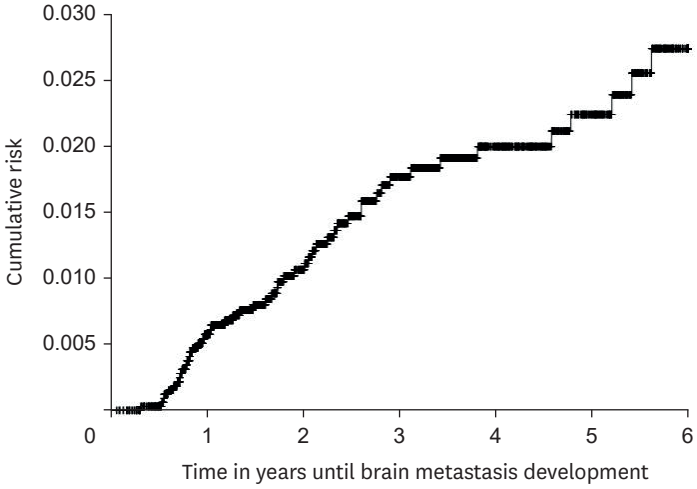


**Fig. 2.** Cumulative risk of developing cerebral metastasis after cervical cancer diagnosis.

meningeal carcinomatosis. No patient displayed CM at the time of CC diagnosis. After a mean follow-up time of 3.2± 2.1 years (range, 21 days to 10 years) a cumulative incidence of 1.5% (95% CI=1.12–1.97) and incidence density at the end of the 6th year of 27.4 per 1,000 women/year were noted (**Table 1**, **Fig. 2**).

**Tables 2** and **3** present the comparisons between demographic, epidemiological, clinical and tumor characteristics according to CM occurrence during the study period. Concerning the univariate analysis, non-squamous histological types, the presence of previous pulmonary, lymphatic or bone metastases, and advanced staging were significantly associated with to CM development risks. In the adjusted analysis, non-squamous histological types led to a higher CM development risk, with neuroendocrine carcinoma comprising the highest risk (OR=21.31; 95% CI=6.65–68.37; p<0.001). Compared to clinical stage I tumors, a 3.15-fold higher risk of CM development was observed in patients presenting stage III tumors (95% CI=1.16–8.58; p=0.025) and a 4.32-fold higher risk noted in patients with stage IV tumors at diagnosis (95% CI=1.34–13.94; p=0.015). The presence of previous pulmonary metastasis increased the risk of CM development in 4.04-fold (95% CI=1.82–8.94; p=0.001) (**Table 4**).

## DISCUSSION

This is the first study to assess CM incidence in patients with CC and its risk factors in Brazil. A total of 3,397 patients with histologically proven epithelial lineage CC were evaluated, with 51 identified as presenting CM, with a cumulative incidence of 1.5% (95% CI=1.12–1.97). Non-squamous histological tumor types, the presence of previous pulmonary metastasis, and stages III and IV at diagnosis were independent factors associated with CM occurrence.

Teke et al. [7] identified 15 CM cases among 820 CC patients, an 1.8% incidence, in a center in Turkey. Hwang et al. [9] reported a lower incidence of 0.45%, observing 11 CM cases among 2,458 CC patients in Korea, from 2001 to 2011. In Italy, Cormio et al. [13] reported a1.18% incidence, comprising 14 CM cases among 1,184 CC patients. Mahmoud-Ahmed et al. [14] reported a 0.47% incidence, indicating 6 CM cases among 1,279 CC patients treated at the Cleveand Clinic. The present study identified an incidence rate of 1.5%, thus compatible with previously described CM incidence rates in CC cases.


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**Table 2.** Baseline demographic and epidemiological characteristics of patients diagnosed with cervical cancer

| Risk factors | Total No. (%*) | Cerebral metastasis | | | p-value |
|---|---|---|---|---|---|
| | | Yes No. (%†) | No No. (%†) | Univariate analysis cOR (95% CI) | |
| Period | | | | | |
| 2010–2013 | 1,878 (55.3) | 28 (1.5) | 1,850 (98.6) | Reference | |
| 2014–2017 | 1,519 (44.7) | 23 (1.5) | 1,496 (98.6) | 1.02 (0.58–1.77) | 0.956 |
| Age (yr) | | | | | |
| <35 | 550 (16.2) | 10 (1.8) | 540 (98.2) | Reference | |
| 35–49 | 1,327 (39.0) | 17 (1.3) | 1,310 (98.7) | 0.70 (0.32–1.54) | 0.376 |
| ≥50 | 1,520 (44.8) | 24 (1.6) | 1,496 (98.4) | 0.87 (0.41–1.82) | 0.705 |
| Ethnicity/skin color | | | | | |
| White | 1,492 (43.9) | 20 (1.3) | 1,472 (98.7) | Reference | |
| Brown | 1,496 (44.0) | 25 (1.7) | 1,471 (98.3) | 1.25 (0.69–2.26) | 0.459 |
| Black | 404 (11.9) | 6 (1.5) | 398 (98.5) | 1.11 (0.44–2.78) | 0.825 |
| Yellow/Indigenous | 5 (0.2) | 0 (0.0) | 5 (100) | ‡ | 0.999 |
| Education level | | | | | |
| ≥8 years | 1,755 (51.6) | 27 (1.6) | 1,728 (98.4) | Reference | |
| <8 years | 1,637 (48.2) | 24 (1.4) | 1,613 (98.6) | 0.95 (0.55–1.66) | 0.863 |
| Missing | 5 (0.2) | 0 (0.0) | 5 (100) | ‡ | 0.999 |
| Marital status | | | | | |
| Living with a partner | 1,255 (37.0) | 20 (1.6) | 1,235 (98.4) | Reference | |
| No partner | 2,025 (59.6) | 31 (1.5) | 1,994 (98.5) | 0.96 (0.54–1.69) | 0.890 |
| Missing | 119 (3.4) | 0 | 119 | ‡ | 0.996 |
| Alcoholic beverage consumption | | | | | |
| Never | 2,698 (79.4) | 39 (1.4) | 2,659 (98.6) | Reference | |
| Ex-consumer | 152 (4.5) | 5 (3.3) | 147 (96.7) | 2.32 (0.90–5.97) | 0.081 |
| Yes | 442 (13) | 7 (1.6) | 435 (98.4) | 1.10 (0.49–2.47) | 0.823 |
| Missing | 105 (3.1) | 0 | 105 | ‡ | 0.997 |
| Smoking | | | | | |
| Never | 1,972 (58) | 30 (1.5) | 1,942 (98.5) | Reference | |
| Ex-consumer | 491 (14.4) | 9 (1.8) | 482 (98.2) | 1.21 (0.57–2.56) | 0.621 |
| Yes | 834 (24.5) | 12 (1.4) | 822 (98.6) | 0.94 (0.48–1.85) | 0.869 |
| Missing | 100 (3.1) | 0 | 100 | ‡ | 0.997 |
| City of origin | | | | | |
| Rio de Janeiro - RJ | 1,441 (42.4) | 21 (1.4) | 1,420 (98.6) | Reference | |
| Other municipalities in the state of RJ | 1,956 (57.6) | 30 (1.5) | 1,926 (98.5) | 1.05 (0.60–1.85) | 0.856 |
| Origin of referral to the cancer center | | | | | |
| Brazilian Unified Health System | 2,851 (83.9) | 42 (1.5) | 2,809 (98.5) | Reference | |
| Other | 546 (16.1) | 9 (1.6) | 537 (98.4) | 1.12 (0.54–2.32) | 0.758 |
| Previous diagnosis and treatment | | | | | |
| No diagnosis and no treatment | 155 (4.6) | 3 (1.9) | 152 (98.1) | Reference | |
| With diagnosis and with or without treatment | 3,242 (95.4) | 48 (1.5) | 3,194 (98.5) | 0.76 (0.23–2.47) | 0.650 |
| Total | 3,397 (100.0) | 51 (1.5) | 3,346 (98.5) | - | - |

cOR, crude odds ratio; CI = confidence interval.
*Column percentages; †Row percentages; ‡Not available.

CC dissemination commonly occurs by direct extension (by contiguity) and lymphatic embolization. Hematogenous dissemination occurs in about 5% of all cases, more common in advanced disease cases, in poorly differentiated tumors and in unusual histological types, such as adenosquamous carcinoma or neuroendocrine tumors, which can present vascular invasion even in early stages [15].

CC incidence and mortality rates have decreased in developed countries, mainly as a consequence of the early detection and treatment of precursor lesions. Conventional screening by cytology seems, however, less effective for adenocarcinoma detection, as increased adenocarcinoma incidence rates have been reported. For example, in Western countries with wide screening coverage, adenocarcinoma cases can represent up to 25% of CC cases. Precursor adenocarcinoma lesions are more difficult to identify compared to

**Table 3.** Baseline clinical and pathological characteristics of patients diagnosed with uterine cervical cancer

| Risk factors | Total No. (%*) | Cerebral metastasis | | | p-value |
|---|---|---|---|---|---|
| | | Yes No. (%†) | No No. (%†) | Univariate analysis cOR (95%CI) | |
| Histology | | | | | |
| Squamous cell carcinoma | 2,656 (78.2) | 23 (0.9) | 2,633 (99.1) | Reference | |
| Adenocarcinoma | 589 (17.3) | 14 (2.4) | 575 (97.6) | 2.79 (1.43–5.45) | **0.003** |
| Adenosquamous carcinoma | 107 (3.15) | 6 (5.6) | 101 (94.4) | 6.80 (2.71–17.07) | **<0.001** |
| Undifferentiated carcinoma | 20 (0.6) | 3 (15) | 17 (85) | 20.20 (5.54–73.70) | **<0.001** |
| Neuroendocrine carcinoma | 25 (0.75) | 5 (20) | 20 (80) | 28.62 (9.89–82.81) | **<0.001** |
| Clinical stage | | | | | |
| I | 864 (25.4) | 5 (0.6) | 859 (99.4) | Reference | |
| II | 1,052 (31.0) | 13 (1.2) | 1,039 (98.8) | 2.15 (0.76–6.05) | 0.147 |
| III | 1,177 (34.6) | 22 (1.8) | 1,155 (98.2) | 3.27 (1.23–8.68) | **0.017** |
| IV | 251 (7.4) | 11 (4.0) | 240 (96.0) | 7.87 (2.71–22.88) | **<0.001** |
| Missing | 53 (1.6) | 0 | 53 | ‡ | 0.998 |
| Primary tumor treatment | | | | | |
| Surgery | 740 (21.8) | 4 (0.5) | 736 (99.5) | Reference | |
| Chemo-radiotherapy | 2,095 (61.7) | 38 (1.8) | 2,057 (98.2) | 3.4 (1.2–9.6) | **0.020** |
| Other | 562 (16.5) | 9 (1.6) | 553 (98.4) | 3.0 (0.9–9.8) | 0.069 |
| Metastasis prior to cerebral metastasis | | | | | |
| None | 2,935 (86.4) | 31 (1.1) | 2,904 (98.9) | Reference | |
| 1 metastasis site | 328 (9.7) | 13 (4.0) | 315 (96.0) | 3.87 (2.00–7.46) | **<0.001** |
| 2 or + metastasis sites | 134 (3.9) | 7 (5.2) | 127 (94.8) | 5.16 (2.23–11.95) | **<0.001** |
| Previous bone and cartilage metastasis | | | | | |
| Yes | 218 (6.4) | 7 (3.2) | 211 (96.8) | 2.36 (1.05–5.31) | 0.037 |
| No | 3,179 (93.6) | 44 (1.4) | 3,135 (98.6) | Reference | |
| Previous lymph node metastasis | | | | | |
| Yes | 140 (4.1) | 6 (4.3) | 134 (95.7) | 3.20 (1.34–7.62) | 0.009 |
| No | 3,257 (95.9) | 45 (1.4) | 3,212 (98.6) | Reference | |
| Previous lung metastasis | | | | | |
| Yes | 137 (4.0) | 12 (8.8) | 125 (91.2) | 7.93 (4.05–15.51) | <0.001 |
| No | 3,260 (96.0) | 39 (1.2) | 3,221 (98.8) | Reference | |
| Previous liver metastasis | | | | | |
| Yes | 58 (1.7) | 1 (1.7) | 57 (98.3) | 1.15 (0.16–8.509) | 0.888 |
| No | 3,339 (98.3) | 50 (1.5) | 3,289 (98.5) | Reference | |
| Previous soft tissue retroperitoneum and peritoneum metastasis | | | | | |
| Yes | 56 (1.6) | 2 (3.6) | 54 (96.4) | 2.49 (0.59–10.49) | 0.214 |
| No | 3,341 (98.4) | 49 (1.5) | 3,292 (98.5) | Reference | |
| Previous metastasis in other locations | | | | | |
| Yes | 78 (2.3) | 2 (2.6) | 76 (97.4) | 1.76 (0.42–7.35) | 0.441 |
| No‡ | 3,319 (97.7) | 49 (1.5) | 3,270 (98.5) | Reference | |
| Total | 3,397 (100.0) | 51 (1.5) | 3,346 (98.5) | - | - |

Statistically significant differences are displayed in bold ($p<0.05$).
cOR, crude odds ratio; CI = confidence interval.
*Column percentages; †Row percentages; ‡Other metastasis locations: other central nervous system locations (n=9), ovary (n=6), colon and rectum (n=5), vulva (n=3), skin (n=2), heart, mediastinum and pleura (n=2), bladder (n=1), pancreas (n=1); ‡Not available.

squamous cell carcinoma lesions. They are, therefore, usually diagnosed later and associated with a worse prognosis [16,17]. In Brazil, a retrospective cohort study conducted between 2000 and 2009 based on hospital cancer record databases included 51,842 CC cases, 87.8% squamous cell carcinoma cases and 12.2% adenocarcinoma cases. The percentage of patients exhibiting adenocarcinomas increased by 55.9% throughout the 10 years of the study, from 10.2% to 15.9% [17]. In the present study, squamous cell carcinomas comprised the main histological type (78.2%), followed by adenocarcinomas (17.3%), adenosquamous carcinoma (3.2%), and neuroendocrine carcinomas (0.8%), reflecting data from developing countries, which still report high squamous cell carcinoma rates and a slight increase in adenocarcinoma cases [4,17].


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**Table 4.** Independent risk factors for cerebral metastasis

| Risk factors | Multivariate analysis | |
|---|---|---|
| | aOR (95% CI) | p-value |
| Histology | | |
| Squamous cell carcinoma | Reference | |
| Adenocarcinoma | 2.90 (1.46–5.75) | **0.002** |
| Adenosquamous carcinoma | 7.33 (2.87–18.73) | **<0.001** |
| Undifferentiated carcinoma | 14.37 (3.77–54.76) | **<0.001** |
| Neuroendocrine carcinoma | 21.31 (6.65–68.37) | **<0.001** |
| Clinical stage | | |
| I | Reference | |
| II | 2.17 (0.77–6.18) | 0.145 |
| III | 3.15 (1.16–8.58) | **0.025** |
| IV | 4.32 (1.34–13.94) | **0.015** |
| Missing | * | 0.997 |
| Previous lung metastasis | | |
| No | Reference | |
| Yes | 4.04 (1.82–8.94) | **0.001** |

Statistically significant differences are displayed in bold ($p < 0.05$).
aOR, adjusted odds ratio; CI = confidence interval.
*Not available.

Adenocarcinomas have been associated with a higher risk of distant recurrence via the hematogenous route, resulting in worse overall and disease-free survival compared to squamous cell carcinoma [18]. In the present study, patients with cervix adenocarcinomas exhibited a 2.9-fold higher risk of developing CM compared to those with squamous cell carcinoma tumors. Similarly, Kim et al. described 10 CM in CC patients in three South Korean centers between 2000 and 2012, with 40% presenting adenocarcinomas [19].

The frequency of adenosquamous carcinoma ranges from 3% to 10% [20], although some series may overestimate this diagnosis, as adenocarcinomas, alongside squamous metaplasia and mucus-secreting adenocarcinomas, can mimic adenosquamous carcinoma. In the present study, the frequency of adenosquamous carcinoma was 3.1%, similar to the rate described by Yordanov et al. [20] in Bulgaria, of 3.2%. Adenosquamous carcinoma increased the risk of CM development by 7.3-fold (95% CI=2.87–18.73). In an American study conducted at Yale University, Gressel et al. [21] reported 6 CM cases in CC patients, 33.3% of which comprised adenosquamous carcinoma and 50% were categorized as in stage IV. Similarly, Mahmoud-Ahmed et al. [14] reported 6 CM cases in CC patients, two adenosquamous carcinoma, one adenocarcinoma and three squamous carcinomas.

Cervical neuroendocrine tumors are rare, accounting for less than 1% of cervical carcinomas, and often exhibit a poor prognosis, as they present early lymphovascular invasion [22]. In a meta-analysis performed by Kato et al. 12.5% of 224 CM patients presented neuroendocrine carcinoma, a much higher percentage than the rates observed in primary lesions [5]. In the present study, neuroendocrine carcinoma was the main risk factor for CM development, increasing the risk by 21-fold (95% CI=6.65–68.37), in agreement with the literature [9,11]. On the other hand, undifferentiated carcinomas also presented a high risk for CM development (OR=14.37; 95% CI=3.77–54.76), although they have been described in few studies due to their rarity [23].

Other studies have formulated hypotheses concerning risk factors for CM development in CC patients. Weed et al., for example, observed a 20% CM rate in patients presenting neuroendocrine carcinoma [11], while Hwang et al., when studying 11 CM cases in CC

patients, observed that 54.5% exhibited non-squamous histological tumor and 90%, distant dissemination, highlighting that the neuroendocrine subtype and pulmonary metastases may be considered risk factors for CM development in CC patients [9]. In the present study, non-squamous histological subtypes, which are highly invasive, accounted for 54.9% of all CM cases, unlike in primary cervical lesions, where squamous cell carcinomas were responsible for 78.7% of all cases. According to the review carried out by Bi and Li [12] non-squamous subtypes account for at least 32% of CM cases, significantly higher than the rates reported for primary cervical lesions. In that review, almost half of all CM patients exhibited advanced-stage disease [12]. Furthermore, as hypothesized by Hwang et al. [9], the present study demonstrated that the presence of previous lung metastasis increases the risk of CM development by 4-fold after adjustment in the multivariate analysis (95% CI=1.82–8.94). Cagney et al. [10] reported that 29.2% of CC patients exhibited pulmonary metastasis synchronous to CM.

So far, the guidelines for the follow-up of CC patients do not recommend CM screening through brain imaging exams, as this is considered a rare event [4], with cranial imaging being usually requested in the presence of acute neurological disorders symptoms, such as focal deficits or seizures. However, insidious or discrete symptoms can be confused with treatment side effects, decreased performance status and metabolic disorders, among others [4], and decisions are based on squamous cell carcinoma comportment, although studies indicate that non-squamous subtypes may present different responses to standard primary tumor treatment. Thus, a personalized follow-up considering histological subtype may reduce the risk of distant metastasis, leading to increased patient survival [21,24].

As a clinical recommendation, we suggest that patients presenting non-squamous histological types should be considered for both therapeutic decision-making and CM screening through cranial imaging exams, as they may present early lymphatic angiolymphatic invasion. As the current cervical cancer treatment is based on staging, considering the results of this study, tumor biology should be considered in the identification of patients at high risk for CM development who could benefit from more aggressive treatments. Considering that only a small number of patients exhibit a hematogenous spread and that tumor subtypes such as adenocarcinomas, neuroendocrine carcinomas and adenosquamous carcinoma and undifferentiated carcinomas are less frequent than squamous carcinomas, CM screening in these cases may be cost effective, as these tumors comprise the highest CM development risks.

This study exhibits noteworthy limitations and strengths. First, these results reflect data from a single specialized cancer treatment institution, which may affect the external validity of the reported results. In addition, as INCA is a reference institution for cancer treatment, over 95% of the cases exhibit a confirmed CC diagnosis upon patient admission. Furthermore, CM incidence rate may have been underestimated, as only patients with brain imaging exams performed at the study institution and available in its image bank were considered as CM cases. As a routine these exams are only performed following medical suspicion and patients often display other clinical conditions that explain neurological symptoms, such as metabolic changes, impairment due to advanced disease or the use of opiates and may progress to death without CM confirmation. Another limitation is the fact that patients with severe acute neurological disorders may seek hospital care at another health unit close to their residence and were not identified in this study. Finally, the adequacy of the primary CC treatment and its impact on the risk of developing cerebral metastasis could not be assessed. However, it is

important to highlight that this is the largest recorded CC patients study assessed with the aim of identifying new CM cases, and all suspected CM cases were reviewed by a radiologist with experience in neuroradiology, thus minimizing possible bias.

In conclusion, a cumulative CM incidence of 1.5% (95% CI=1.12–1.97) was observed herein, with a higher incidence density in the first year after CC diagnosis and a progressive decrease in risk up to the 6th year of follow-up. Histological type, the previous presence of pulmonary metastasis and distant dissemination were the main CM risk factors in CC patients.

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