Brain metastases from cervical cancer reduce longevity independent of overall tumor burden

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ABSTRACT

**Background:** Isolated brain metastasis (IBM) from cervical cancer is a very rare encounter in neurosurgery. We sought to understand how patients with isolated brain metastases differ from those with metastases in the setting of widespread disease.

**Methods:** A systematic review was completed using PubMed and the Cochrane Library. Patients with isolated brain metastases (IBM) and non-isolated brain metastases (NIBM, or brain metastases in the setting of disseminated disease), were compared. Two-sided statistical tests were used to determine significance. Survival function was carried out using the Kaplan–Meier method.

**Results:** A total of 89 patients, 25 with IBM and 64 with NIBM, were identified. The time interval between initial diagnosis of cervical cancer and diagnosis of brain lesion was significantly shorter in the IBM group (median 7.5 vs. 20.05 months, and IBM vs. NIBM, respectively; \(P = 0.006\)). Overall survival from initial diagnosis of cervical cancer was significantly shorter for the IBM group versus the NIBM group (7.63 vs. 26.3 months, respectively; \(P = 0.0005\)). Data demonstrate a 3.4-fold reduction of median life expectancy to 7.63 months.

**Conclusion:** Taken together, our data suggest that for cervical cancer patients with brain metastasis intracranial metastasis itself (and not overall tumor burden) represent a sentinel event in limiting longevity. While the present study is underpowered to compare treatment options directly, further work should be focused on determining the optimal treatment for these patients.

**Keywords:** Brain, Cancer, Cervical, Cervix, Isolated, Metastases, Non-isolated, Survival, Uterine, Uterus

INTRODUCTION

Cervical cancer is an aggressive gynecological cancer of the uterine cervix. Tumors may consist of one of many histopathologies, from the more common squamous or adenocarcinomatous tumors to less
common neuroendocrine tumors. While incidence in the US has decreased due to the widespread screening of cervical cytology and adoption of the human papillomavirus vaccine, prevalence remains at a value of roughly 6.8 cases per 100,000 women per year.\textsuperscript{[6]} However, cervical cancer continues to be a leading cause of cancer death in women in less developed countries. Metastases are common, especially in late-stage disease. Among the more frequent sites of distant metastasis are the lungs (21%), para-aortic nodes (11%), and abdominal cavity (8%).\textsuperscript{[14]}

Brain metastasis represents a rather uncommon but known complication. The estimated frequency of brain metastases from cervical cancer seen in the clinical setting ranges from 0.4% to 2%, while autopsy studies have reported brain metastases in 3–10% of cervical cancer patients.\textsuperscript{[4,10,40]} Most patients with cervical cancer brain metastases present at a time of widespread systemic disease and with poor prognosis. Still, other patients may present with isolated brain metastases. To this end, isolated brain metastasis (IBM) from cervical cancer is defined as tissue-confirmed metastasis to the brain without radiographic evidence of metastases to any other region at the time of diagnosis. Given its relative rarity, cervical cancer IBM remains poorly characterized. It remains unclear if IBM represents a distinct clinical entity from NIBM. Previous reports\textsuperscript{[11]} have suggested that overall tumor burden, and not the development of brain metastasis, is the key determinant in survival for gynecological cancer. Understanding different disease course, should it exist, is critical in therapeutic planning and managing expectations of patients and their families. Toward better understanding, IBM and NIBM in cervical cancer, we conducted a literature review and meta-analysis. Our review of the literature revealed 24 reports of IBM from primary cervical cancer. It remains unclear if patients who present with IBM or the respective primary disease in cervical cancer patients presenting as IBM differs from those observed in patients with non-isolated brain metastases (NIBM) – that is to say, brain metastases in the setting of disease disseminated to other organ systems. We set out to study several parameters including patient characteristics, tumor characteristics, treatments received, and survival between patients with IBM to those with NIBM. This systematic review serves to determine possibly identify differences by comparing 25 cases of IBM to 64 cases of NIBM. The 25 cases consist of 24 cases found in the literature, and one case that presented to our institution. Although other cases of IBM and NIBM from cervical cancer have been reported, many reports neglect to report key details about the cases and could not be included in this study.

**MATERIALS AND METHODS**

A review of the published literature before August 2018 was conducted using biomedical databases PubMed, OVID, Medline, Web of Knowledge, and EMBASE. We sought peer-reviewed articles on brain metastasis. Terms for the search included “brain metastases,” “isolated brain metastases,” “cervical cancer metastases,” “cervical cancer brain metastases,” and “uterine cervical cancer brain metastases.” The search was temporally restricted to 35 years, between 1983 and 2018, to ensure cases contained those followed with modern computed tomography scanning. Exclusion criteria were directed at removing low-quality case reports and case series, operationally defined as publications not meeting 8/10 of Joanna Briggs Institute (JBI) criteria for case series, or 6/8 JBI criteria for case reports (as applicable). PRISMA guidelines were followed for reporting the qualitative results. The decision to involve or eliminate all relevant articles and data extraction was completed by the authors, and any controversies and disagreements were settled by discussion.

**Inclusion criteria**

All studies with one or more cases of cervical cancer with brain metastases with details specific to each patient were included, such as histology, stage, survival, and treatment.

**Exclusion criteria**

Articles presenting at autopsy, in vitro studies, and any animal studies were excluded from the study. In addition, articles were excluded if the extent of metastases (isolated to brain versus systemic) was not specified. Cases without details of survival were not included in our analysis. Further, duplicate articles in these databases and full-text articles not written in English were also screened and excluded. Similarly, opinion letters, short reviews, very old case reports, and studies with the possibility of blurred/mixed and confusing data were excluded from the study.

**Data extraction**

The following characteristics were collected and analyzed: patient age, disease interval (time between diagnosis of cervical cancer and discovery of brain metastasis), clinical presentation, histopathology, location of brain lesions, treatment, and survival.

**Statistical analysis**

Wilcoxon Rank-Sum tests were performed on median data; Fischer’s exact tests were performed across frequency data. As is common practice, a significance threshold was set at $P < 0.05$. Survival was determined using the Kaplan–Meier analysis with a 95% confidence interval. Identifying information for patients alive at the time of publication of the respective articles was censored in the statistical analysis. All data were analyzed by custom scripts written in MATLAB.
RESULTS

We identified 238 articles using the selected keywords, and 45 articles matched the topic of cerebral metastases from cervical cancer. Of these articles, 36 articles regarding cervical cancer with brain metastasis published between 1983 and 2018 met the study criteria and included granular patient data with information regarding survival. Twenty-five patients with IBM and 64 patients with NIBM were identified. The mean age in patients with IBM was 48.5 (range ± 11.6 years) and NIBM 49.1 (range ± 11.8 years) was not significantly different (P = 0.83). Cancer stage at the time of diagnosis of brain metastasis did not differ significantly between groups (mean stage IBM 2.1, NIBM 2.2, P = 0.71). The interval between cervical and brain lesion diagnosis was significantly shorter in the IBM group (7.5 months vs 20.05 months, IBM vs. NIBM, respectively; P = 0.006). Comparisons between IBM and NIBM are summarized in Table 1.[1-4,6-10,12-19,21-35] IBM and NIBM patient case details from previous studies are displayed in Table 2[3,5,7-10,13,17,18,22,25,26,28,31,32,34,36-39,41,43] and Table 3,[1,4,7,8,10,13,17,18,22,25,26,28,31,32,34,36-39,41,43] respectively.

Histopathology

Squamous cell carcinoma was the most common histopathology in both groups followed by adenosquamous and neuroendocrine tumors. The type of histology did not differ significantly between the two groups [Table 1].

Treatment

Radiation therapy was the most often used treatment for primary cervical cancer in both groups (56%, 14/25 IBM; 54%, 30/56 NIBM); the standard of care for radiotherapy in locally advanced cervical cancer is external-beam radiotherapy or cervical brachytherapy; institutional, patient, and provider preference largely determine modality usage. Surgical resection (total abdominal hysterectomy) was used in 32% (8/25) of patients with IBM and 39% (22/56) of patients with NIBM. About 48% (12/25) of patients with IBM and 30% (16/54) of patients with NIBM underwent surgical resection of brain metastases, while 52% (13/25) of IBM patients and 87% (47/54) of patients with NIBM underwent whole-brain radiation therapy [Table 1]. Notably, treatment for initial cervical lesion did not differ between groups, yet IBM patients received statistically more frequent surgical monotherapy (24% vs. 6%, P = 0.044) and statistically less frequent whole-brain radiation monotherapy (20% vs. 59%, P = 0.0026) than NIBM patients.

Survival

We examined two separate time intervals: survival time from diagnosis of initial cervical cancer, and survival time from diagnosis of brain metastasis. The median overall survival from the time of initial diagnosis of cervical cancer was significantly shorter in IBM versus NIBM [IBM 7.63 months; NIBM, 26.3 months; P = 0.0005; Table 1 and Figure 1]. Survival after diagnosis of brain metastases did not differ between groups (median, IBM 7 months vs. NIBM 4 months, P = 0.08). The Kaplan–Meier analysis revealed 75, 50, and 25% overall survival for IBM to be 3.1, 7.63, and 14 months versus 13.6, 26.3, and 55.3 months in NIBM [Figure 2]. Across all treatments examined, NIBM patients survive longer than IBM patients from time of diagnosis of the initial lesion [Table 4]. After a diagnosis of brain lesion, survival is similar despite treatment [Table 4]. To further support this analysis, we performed pair-wise analysis, matching IBM patients to those of identical histology, stage, and age (±10 years, where possible). This analysis is in agreement with overall treatment-group analysis (median survival since cervical cancer diagnosis, 7.63 months IBM; 25.5 months NIBM, P = 0.0046).

Temporal analysis showed that there is no significant effect from changing treatment modalities on patient outcomes over the years from which studies were collected [Supplemental Table 1].

DISCUSSION

Metastasis to the brain from cervical cancer is not common in clinical neurosurgical practice. As such, the possibility of brain metastasis is often not considered until there is evidence of neurological deficit. Based on data from the
National Cancer Institute from 2009 to 2013, squamous cell carcinomas comprised 64% of all cervical cancers while adenocarcinomas comprised 15.1% and adenosquamous carcinomas comprised 3.4% of all reported cervical
Table 2: Characteristics of individual patients with isolated brain metastases.

| First author                      | Age | Type of cancer | Stage | Survival from dx of brain metastases | Interval time (mo) | Survival from dx of cervical ca (mo) | Initial Tx | Tx for brain metastases | Radiation dose (brain) |
|-----------------------------------|-----|----------------|-------|--------------------------------------|-------------------|--------------------------------------|------------|------------------------|------------------------|
| Brown 2007[6]                     | 60  | Adenosquamous  | IB2   | 5                                    | 0.5               | 5.5                                  | RH, BSO, LND | SX/SRS/CTX             | 16 Gy                  |
| Sato 2015[7]                      | 50  | Squamous       | NR    | 7                                    | 0                 | 7                                    | CCRT       | SX/WBRT/SRS/CTX         | 24 Gy                  |
|                                   | 42  | Adenosquamous  | IB     | 22.5                                 | 0.25              | 22.75                                | XRT        | 2 SRS only              | 18 Gy                  |
|                                   | 46  | Squamous       | IIIB   | 10.5                                 | 2.5               | 13                                   | TAH, BSO, XRT | 5 WBRT only            | 37.5 Gy                |
|                                   | 41  | Adenosquamous  | IIIB   | 8.25                                 | 12                | 20.25                                | XRT        | 2 WBRT only             | 37.5 Gy                |
|                                   | 69  | Squamous       | IVB    | 7.25                                 | 0                 | 7.25                                 | None       | nan WBRT/SRS            | 30 Gy, 9 Gy            |
| Mahmoud-Ahmed 2001[8]             | 43  | Squamous       | IIB    | 7                                    | 18.5              | 25.5                                 | XRT        | 2 WBRT/SRS              | 35 Gy, 24 Gy           |
| Chura 2007[9]                     | 55  | Squamous       | IB1    | 7.9                                  | 1.1               | 9                                    | RH, BSO, LND, CTX | 7 WBRT/SRS/CTX         | 40 Gy, 17.5 Gy         |
| Pyeon 2014[10]                    | 44  | Large Cell NE  | NR     | 7                                    | 8                 | 15                                   | TAH, CTX   | 7 WBRT                  | NR                     |
| Marongiu 2012[11]                 | 48  | Squamous       | RPA I  | 11                                   | 60                | 71                                   | NR         | nan SX/WBRT             | NR                     |
| Amita 2005[12]                    | 54  | Squamous       | IIA    | 6                                    | 6                 | 12                                   | CTX, XRT   | 6 SX only               | NR                     |
| Robinson 1997[13]                 | 68  | Squamous       | IIIB   | 100                                  | 28                | 128                                  | CCRT       | 4 SX/WBRT/SRS           | 30 Gy, 10 Gy           |
| Gupta 2016[14]                    | 52  | Adenocarcinoma | NR     | 6                                    | 0                 | 6                                    | NR         | nan SX only             | NA                     |
| Cormio 1999                       | 49  | Squamous       | IB     | 10                                   | 29                | 10                                   | TAH, LND   | 1 SX only               | NA                     |
| isolated                          | 48  | Adenocarcinoma | IIIB   | 3                                    | 7                 | 3                                    | CTX, XRT   | 4 WBRT only             | NA                     |
| Kumar isolated                    | 50  | Squamous       | IIIB   | 7                                    | 35                | 7                                    | XRT        | 2 SX only               | NA                     |
| Omari-Alaoui isolated             | 67  | Squamous       | IIB    | 2                                    | 9                 | 2                                    | XRT        | 2 WBRT only             | 30 Gy                  |
| isolated                          | 33  | Small cell NE  | IA     | 1                                    | 1                 | 1                                    | RH+CTx+RTx | 5 SRS only              | 18 Gy                  |
| Chung                             | 79  | Squamous       | IB1    | 3.1                                  | NA                | 3.1                                  | TAH, XRT   | 5 SRS only              | 8 Gy                   |
| Huang                             | 43  | Adenosquamous  | IIB    | 1.2                                  | NA                | 1.2                                  | TAH, XRT, CTX | 6 SRS only             | 25 Gy                  |
| Cordeiro                          | 31  | Adenocarcinoma | IIB    | 1                                    | 24                | 1                                    | TAH        | 1 SX/WBRT               | NA                     |
| Current study                     | 50  | Squamous       | IIB    | 2                                    | 6                 | 8                                    | CTX, XRT   | 4 SX only               | NA                     |

dx: Diagnosis, mo: Months, ca: Carcinoma, NE: Neuroendocrine, RPA: Recurrent partitioning analysis classification, Tx: Treatment, CCRT: Adjuvant concurrent chemoradiation therapy, XRT: Radiation therapy, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, LND: Lymph node dissection, CTX: Chemotherapy, NR: Not reported, RH: Radical hysterectomy, Gy: Gray, WBRT: Whole brain radiation, Sx: Surgery, SRS: Stereotactic radiosurgery
| First author | Age | Type of cancer | Stage | Survival since dx of brain metastases (mo) | Interval time (mo) | Survival from time of cervical cancer dx (mo) | Initial Tx | Initial tx, coded | Tx for Brain Metastases | Met tx, coded | Radiation dose (brain) |
|--------------|-----|----------------|-------|------------------------------------------|------------------|-------------------------------------------|-------------|----------------|-------------------------|--------------|----------------------|
| Nagar 2005   | 72  | Adenocarcinoma | IIA   | 0.5                                      | 9                | 9.5                                       | TAH, BSO, XRT, CTX | 5             | WBRT                   | 2           | 30 Gy                |
| Mahmoud 2001 | 45  | Adenocarcinoma | IIIB  | 0.5                                      | 75               | 75.5                                      | TAH, BSO, XRT, CTX | 5             | WBRT                   | 2           | 27 Gy                |
| Erdis 2011   | 67  | Squamous       | IVB   | nan                                      | –                | nan                                       | CTX         | 3             | –                       | nan          | –                    |
| Setoodeh 2012| 53  | Squamous       | –     | nan                                      | 0                | nan                                       | –           | nan           | SX                      | 1           | –                    |
| Gressel 2015 | 52.2| Squamous       | I     | 3                                         | –                | nan                                       | –           | nan           | 4 XRT                   | 4           | –                    |
| Peters 2010  | 38  | Squamous       | IIB   | nan                                      | –                | nan                                       | CTX, XRT    | 4             | SX                      | 1           | –                    |
|             | 47  | Squamous       | IB1   | 1.5                                      | 16.4             | 17.9                                      | CTX         | 3             | WBRT                   | 2           | 37.5 Gy              |
|             | 30  | Squamous       | IB1   | 3.9                                      | 85.8             | 89.7                                      | RH, LND, XRT | 5             | WBRT                   | 2           | 37.5 Gy              |
|             | 40  | Adenocarcinoma | IB2   | 0.6                                      | 25.4             | 26                                        | RH, BSO, LND | 1             | WBRT                   | 2           | 33 Gy                |
|             | 34  | Squamous       | IIB   | 0.4                                      | 18.6             | 19                                        | TAH, BSO, CTX | 5             | None                   | nan         | –                    |
|             | 29  | Squamous       | IIIB  | 4.4                                      | 24.6             | 29                                        | CTX, RH, BSO, LND, XRT | 5      | WBRT, SRS             | 2           | 38 Gy+17 Gy          |
|             | 34  | Adenosquamous  | IB1   | 6.2                                      | 96.1             | 102.3                                     | RH, LND     | 1             | SX, WBRT               | 4           | 30 Gy                |
|             | 36  | Adenocarcinoma | IIB   | 3.3                                      | 16               | 19.3                                      | CTX         | 3             | None                   | nan         | –                    |
|             | 53  | Adenocarcinoma | IIIA  | 3                                         | 16              | 19                                        | CTX         | 3             | WBRT                   | 2           | 30 Gy                |
|             | 47  | Squamous       | IB1   | 1.1                                      | 2.9             | 4                                         | RH, BSO, LND, CTX, XRT | 6      | WBRT, SRS             | 2           | 40 Gy+17.5 Gy         |
| Chura 2007   | 48  | Squamous       | IIB   | 0.5                                      | 27.9             | 28.4                                      | CTX, XRT    | 4             | None                   | nan         | –                    |
| Park 2010    | 57  | Squamous       | IVB   | 0.3                                      | 6.4              | 6.7                                       | CTX         | 3             | WBRT                   | 2           | 30 Gy                |
|             | 45  | Squamous       | IB2   | 6                                         | 30              | 36                                        | TAH, XRT    | 5             | WBRT                   | 2           | 30 Gy                |
|             | 59  | Squamous       | IIB   | 5.9                                      | 12.3             | nan                                       | CCRT        | 4             | WBRT                   | 2           | –                    |
|             | 52  | Adenosquamous  | IIB   | nan                                      | 19.6             | nan                                       | CCRT        | 4             | CTX                    | 3           | –                    |
|             | 75  | Squamous       | IIIB  | nan                                      | 51.2             | nan                                       | CCRT        | 4             | SX, WBRT               | 4           | –                    |
|             | 47  | Squamous       | IIIA  | nan                                      | 5.4             | nan                                       | CCRT        | 4             | WBRT                   | 2           | –                    |
|             | 58  | Small cell     | –     | nan                                      | 83.3             | nan                                       | CCRT        | 4             | CTX                    | 3           | –                    |
|             | 44  | Squamous       | IVB   | nan                                      | 3.4             | nan                                       | CTX         | 3             | WBRT                   | 2           | –                    |
|             | 50  | Small cell     | IB    | nan                                      | 34.1             | nan                                       | RH          | 1             | CTX                    | 3           | –                    |
|             | 41  | Adenocarcinoma | IVB   | nan                                      | 4.9             | nan                                       | CCRT        | 4             | WBRT                   | 2           | –                    |
|             | 33  | Adenocarcinoma | IVB   | nan                                      | 15.4             | nan                                       | CTX         | 3             | WBRT                   | 2           | –                    |
|             | 47  | Squamous       | IIIB  | nan                                      | 5.4             | nan                                       | CCRT        | 4             | WBRT                   | 2           | –                    |
### Table 3: (Continued)

| First author | Age | Type of cancer | Stage | Survival since dx of brain metastases | Interval time (mo) | Survival from time of cervical cancer dx | Initial Tx | Initial tx, coded | Tx for Brain Metastases | Met tx, coded | Radiation dose (brain) |
|--------------|-----|----------------|-------|--------------------------------------|-------------------|----------------------------------------|-----------|-------------------|------------------------|-------------|------------------------|
| Hwang 2013  | 74  | Adenocarcinoma | –     | nan                                  | 49                | nan                                    | RT        | 2                 | None                   | nan          | –                      |
| 41           |     | Squamous      | IIB   | 7.5                                  | 6.1               | 13.6                                   | XRT       | 2                 | WBRT                   | 2            | 30 Gy                  |
| 41           |     | Undifferentiated carcinoma |      | 4.1                                  | 61.8              | 65.9                                   | OP*, XRT  | 5                 | WBRT                   | 2            | 35 Gy                  |
| 66           |     | Adenocarcinoma | IIB   | 10.3                                 | 28.7              | 39                                     | XRT       | 2                 | WBRT                   | 2            | 30 Gy                  |
| 54           |     | Adenocarcinoma | IIB   | 1.9                                  | 8.9               | 10.8                                   | OP*       | 1                 | WBRT                   | 2            | 40 Gy                  |
| 60           |     | Squamous      | IIB   | 1.8                                  | 53.5              | 55.3                                   | OP*, XRT  | 2                 | WBRT                   | 2            | 40 Gy                  |
| 73           |     | Squamous      | IIB   | 12.3                                 | 14.3              | 26.6                                   | OP*       | 1                 | WBRT                   | 2            | 40 Gy                  |
| 36           |     | Squamous      | IBl   | 2                                    | 20.5              | 22.5                                   | OP*, XRT  | 2                 | WBRT                   | 2            | 30 Gy                  |
| Ikeda 1998   | 59  | Squamous      | IB2   | 22.6                                 | 33.8              | 56.4                                   | OP*, XRT  | 2                 | WBRT                   | 2            | 40 Gy                  |
| Tajran 2003  | 59  | Adenocarcinoma | IB    | 4.5                                  | 96                | 100.5                                  | BSO, LND  | 1                 | SX, WBRT               | 4            | 45 Gy                  |
| Lefkowitz 1983 | 68 | Adenocarcinoma | IIB   | nan                                  | 7                 | nan                                    | XRT       | 2                 | WBRT                   | –            | –                      |
| Agrawal 2007 | 49  | Squamous      | IIB   | nan                                  | 36                | 36                                     | XRT       | 2                 | SX                     | 1            | –                      |
| Branch 2014  | 46  | Squamous      | IB    | 29                                   | 60                | nan                                    | TAH, CTX, XRT | 5     | SX, WBRT               | 4            | 50 Gy                  |
| Gaussman 2006 | 36 | Squamous      | IB    | 96                                   | 36                | 96                                     | TAH, CTX  | 7                 | SX, WBRT               | 4            | 40 Gy                  |
| Ziainia 1999 | 38  | Squamous      | –     | 4                                    | 4                 | 8                                      | XRT, CTX  | 4                 | WBRT                   | 2            | 35 Gy                  |
| 47           |     | Squamous      | IIA   | 13.8                                 | –                 | nan                                    | RH, CTX, XRT | 66 | SRS                   | 2            | 12 Gy                  |
| 40           |     | Squamous      | IA2   | 4.6                                  | –                 | nan                                    | TAH, CTX, XRT | 6     | SRS, WBRT             | 2            | 10 Gy                  |
| 47           |     | Adenocarcinoma | IB    | 1.2                                  | –                 | nan                                    | TAH, CTX, XRT | 6     | SRS, WBRT             | 2            | 9 Gy                   |
| 62           |     | Squamous      | IIB   | 10.8                                 | –                 | nan                                    | TAH, CTX, XRT | 6     | SRS, WBRT             | 2            | 9 Gy                   |
| 63           |     | –             | –     | 9.3                                  | –                 | nan                                    | CTX, XRT  | 4                 | SRS, WBRT*             | 2            | 14 Gy                  |
| 50           |     | –             | –     | 5.5                                  | –                 | nan                                    | TAH, CTX, XRT | 6     | SRS, WBRT*            | 2            | 15 Gy                  |
| 47           |     | Small cell    | –     | 9                                    | –                 | nan                                    | TAH, CTX, XRT | 6     | SRS                   | 2            | 16 Gy                  |
| 52           |     | Squamous      | IIB   | 15.9                                 | –                 | nan                                    | RH, CTX, XRT | 6     | SRS                   | 2            | 17 Gy                  |
| 61           |     | Squamous      | IIA   | 3.8                                  | –                 | nan                                    | CTX, XRT  | 4                 | SRS                    | 2            | 16 Gy                  |
| Chung 2013   | 54  | Squamous      | IB2   | 4.3                                  | –                 | nan                                    | TAH, CTX, XRT | 6     | SRS, WBRT             | 2            | 10 Gy                  |
| Siedel 1988  | 37  | Carcinoid     | IB    | 0.66                                 | 48                | nan                                    | TAH, CTX  | 7                 | WBRT                   | 2            | 27 Gy                  |
| Tenjarla 2014 | 45 | Squamous      | –     | 1                                    | 0                 | 1                                      | None      | nan               | WBRT                   | 2            | 30 Gy                  |
| Rhiem 2007   | 40  | Squamous      | IB    | 2                                    | 12                | 20                                     | TAH, XRT, CTX | 6     | WBRT                  | –            | –                      |

dx: Diagnosis, mo: Months, ca: Carcinoma, NE: Neuroendocrine, RPA: Recurrent partitioning analysis classification, Tx: Treatment, CCRT: Adjuv therapy, XRT: Radiation therapy, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, LND: Lymph node dissection, CTX: Chemotherap hysterectomy, Gy: Gray, WBRT: Whole brain radiation, Sx: Surgery, SRS: Stereotactic radiosurgery, op: Operation with type of resection n

Table 3: (Continued)
cancers.\textsuperscript{[19]} Our own data reflect this distribution, with squamous cell carcinoma being the most common in both IBM (60%) and NIBM (66%).

Many patients are at an advanced stage of the disease by the time brain lesions are diagnosed. Still, in this comparative analysis, 28.7% of patients with metastatic brain disease from primary cervical cancer were found to have no other distant metastases. Histopathology, patient age, symptomatology, and location of metastases were not significantly different between patients with isolated and NIBM.

At present, routine brain imaging is not a part of the guidelines for surveillance of post-treatment cervical cancer patients as issued by the American Society of Clinical Oncology or the National Comprehensive Cancer Network because of the very low incidence of brain metastases in gynecological cancer patients.\textsuperscript{[11,12]} While patients who present with focal neurologic deficits may be quickly diagnosed due to prompt brain imaging, vague symptoms such as headache are the most frequent presentation (40–50% vs. 20–40% for focal neurologic deficits).\textsuperscript{[16]} Patients presenting with milder symptoms may initially have those symptoms mistaken for the side effects of chemotherapy or other forms of treatment.\textsuperscript{[16]} This raises the possibility that brain metastases from cervical cancer may be currently underdiagnosed. We recommend holding a high index of suspicion for sentinel symptoms in patients with any cancers, including gynecological types, which may lead to earlier diagnosis and treatment of brain metastases.

The average age of patients with IBM in the present study was 48.5 years with no significant difference from the age in patients with NIBM (49.1 years). This distribution is consistent with previous reviews\textsuperscript{[4,18,22,29]} with average ages ranging from 48 to 52 years old.

We found the overall median survival from diagnosis of brain metastasis across both groups was 4.6 months, similar to Teke \textit{et al}.’s finding of 4.1 months.\textsuperscript{[40]} Survival after diagnosis of brain metastasis did not differ significantly, while overall survival after an initial diagnosis of cervical cancer was significantly shorter in the IBM group. This is in contrast to previous work\textsuperscript{[11]} which found that survival after brain metastasis was greater in patients with IBM. As prior studies\textsuperscript{[11]} grouped together multiple gynecological cancers, we believe distinct tumor biology of cervical versus other gynecological (i.e., ovarian) tumors may account for some of this difference. The rest of this counterintuitive finding may be explained by a lead-time bias effect, in which irrespective of tumor burden, brain metastasis limits longevity. In IBM, brain metastasis occurs early in disease course; in NIBM, it occurs later. Still, the overall effect in the context of IBM is to reduce lifespan from the time of initial cervical cancer diagnosis.

It is important to keep in mind, however, that as with all meta-analyses our current work may suffer from publication bias – that is to say, isolated brain metastases from cervical cancer are relatively rare and may, therefore, be seen as more reportable. However, we find the result that patients with IBM have reduced overall survival relative to NIBM patients despite the inherently greater disease burden of NIBM patients to be counterintuitive and interesting on its face. While outside the scope of the present study, one must wonder if IBM patients suffer from molecular and/or genetically distinct tumors than those with NIBM. We suggest two paths forward to answer this question: (1) a population-based prospective study to confirm or challenge the results of this meta-analysis, and (2) a molecular biological study of tumor samples from case-matched IBM and NIBM patients. In addition, the cumulative intracranial volume has been shown to be a prognostic factor for brain

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**Figure 2:** Kaplan–Meier analysis of survival from time of diagnosis of brain metastases.

**Table 4:** Treatment subgroup analysis.

| Treatment subgroup analysis | IBM          | NIBM         | \(P\)-value |
|----------------------------|--------------|--------------|-------------|
| Survival since diagnosis   |              |              |             |
| Surgery                    | 5.5 (1–10)   | 26.6 (10.8–102.3) | 0.035* |
| Radiation                  | 20.25 (2–25.5)| 37.5 (13.6–56.4)  | 0.082      |
| Survival since metastasis  |              |              |             |
| Radiation                  | 6.5 (1–22.5) | 4 (0.3–22.6)  | 0.38        |
metastases from renal cell carcinoma.[2] Future studies may investigate whether this is true in brain metastases from cervical cancer as well. Future studies may also examine which patients are most likely to benefit from specific brain metastases treatments from specific treatments. A scoring system such as the Score Index for Stereotactic Radiosurgery for Brain Metastases may be used to determine who is most likely to benefit from SRS based on factors including age, number of lesion, and largest lesion volume.[2] Future studies may evaluate whether this scoring system can be used in patients with cervical brain metastases for a better prediction of prognosis.

CONCLUSIONS

We have reviewed 25 cases of IBM from cervical cancer and have compared patient characteristics, treatment, and survival to data obtained from 64 cases of NIBM in cervical cancer. We found that the two groups have similar overall survival after brain metastasis, but as metastasis occur earlier in IBM, this group has reduced overall survival compared to NIBM in our pooled analysis. This runs somewhat counter to the notion that mortality is in part a function of overall tumor burden. It should aid neurosurgeons and other care providers in treatment planning and managing patient expectations.

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Conflicts of interest

There are no conflicts of interest.

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Supplemental Table 1: Temporal Analysis.

| Group                        | Slope  | Intercept | r-squared | P-value |
|------------------------------|--------|-----------|-----------|---------|
| NIBM - since metastasis      | 0.0875 | -167.81   | 0.0011    | 0.834   |
| IBM - since metastasis       | -1.51  | 3039      | 0.198     | 0.0837  |
| NIBM - since diagnosis       | -0.801 | 1641      | 0.014     | 0.5     |
| IBM - since diagnosis        | -1.5   | 3205      | 0.11      | 0.199   |