Cervical cancer metastasis to the brain: A case report and review of literature

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Abstract

Background: Intracranial metastasis from cervical cancer is a rare occurrence.

Methods: In this study we describe a case of cervical cancer metastasis to the brain and perform an extensive review of literature from 1956 to 2016, to characterize clearly the clinical presentation, treatment options, molecular markers, targeted therapies, and survival of patients with this condition.

Results: An elderly woman with history of cervical cancer in remission, presented 2 years later with a right temporoparietal tumor, which was treated with surgery and subsequent stereotactic radiosurgery (SRS) to the resection cavity. She then returned 5 months later with a second solitary right lesion; she again underwent surgery and SRS to the resection cavity with no signs of recurrence 6 months later. According to the reviewed literature, the most common clinical presentation included females with median age of 48 years; presenting symptoms such as headache, weakness/hemiplegia/hemiparesis, seizure, and altered mental status (AMS)/confusion; multiple lesions mostly supratentorially located; poorly differentiated squamous cell carcinoma; and additional recurrences at other sites. The best approach to treatment is a multimodal plan, consisting of SRS or whole brain radiation therapy (WBRT) for solitary brain metastases followed by chemotherapy for systemic disease, surgery and WBRT for solitary brain lesions without systemic disease, and SRS or WBRT followed by chemotherapy for palliative care. The overall prognosis is poor with a mean and median survival time from diagnosis of brain metastasis of 7 and 4.6 months, respectively.

Conclusion: Future efforts through large prospective randomized trials are warranted to better describe the clinical presentation and identify more effective treatment plans.

Key Words: Brain metastasis, cervical cancer, intracranial metastasis

INTRODUCTION

Cervical cancer is one of the most malignant cancers affecting women, second only to breast cancer.[16] Each year in the United States, approximately 12,000 women are diagnosed with cervical cancer with an estimated 4000 deaths.[6] Cervical cancer typically spreads locally via the lymphatic system to the pelvic and para-aortic
lymph nodes; however, it can metastasize to more distant organs—commonly the lung, liver, bone, and supraclavicular lymph nodes—via the hematogenous pathway.[2,3] Some attribute circulatory patterns for the organ-specific spread, while certain tumor cells are thought to migrate based on attraction to certain surrounding environments—called the “seed and soil” hypothesis; distant spread of cancer is more recently thought of as a multistep process known as the “metastatic cascade.”[41] One study found a 5.3-fold greater risk of death for patients with hematogenous metastasis compared to those with lymphatic metastasis.[25] The 5-year survival for metastatic cervical cancer is only 16.5% compared to 91.5% for localized cervical cancer.[29,48] Early stage or locally advanced cervical cancer is treated with a combination of surgery, chemotherapy, and radiotherapy; however, there is no standard treatment for patients with metastatic cervical cancer, and the goal is usually palliative.[29] Median survival of patients with metastatic cervical cancer is only 8–13 months.[29,48]

Brain metastasis from cervical cancer is a rare occurrence. With only approximately 100 cases of reported intracranial metastases of cervical cancer in the literature, proper management of these patients remains unclear.[2,6] Presence of tumor cells in cerebral circulation does not necessarily lead to metastatic disease; it largely depends on the host’s immune system, number of tumor emboli, tissue neovascularization, and characteristics of the tumor.[2,3] Metastasis to brain has been postulated to occur after spread to the lungs.[6] This is supported by reports that the lungs are the most common area for metastatic cervical cancer; in addition, this pattern of spread is very typical in other types of systemic cancers, such as lung cancer, breast cancer, and melanoma.[6,21] However, there were some reported cases of patients with intracranial metastases from cervical cancer without lung metastases. We described a case of isolated solitary cervical cancer metastasis to the brain and reviewed the literature to characterize more clearly the clinical presentation, treatment, and prognosis of patients with this condition.

**CASE REPORT**

A 75-year-old female with a history of stage IIIIB squamous cell cancer of the cervix, which had been treated and in remission for about 2 years, presented in February 2016 with several weeks of decreased coordination and decreased balance with weakness and clumsiness noted especially on her left side in addition to a left facial droop. Magnetic resonance imaging (MRI) of her brain showed a solitary 4.6 cm × 3.4 cm × 4.1 cm heterogeneous solid mass at the right temporo-parietal junction with surrounding edema, mass effect, and early uncal herniation suggestive of either a metastasis or high-grade primary lesion [Figure 1a and b]. Computed tomography (CT) of her abdomen and pelvis did not show any primary or metastatic lesion. The patient received dexamethasone, which improved her symptoms, and then underwent surgical resection of the tumor in March 2016. Histopathological examination of the resected tumor revealed an epithelial neoplasm with squamous differentiation and extensive keratinization. The tumor cells displayed considerable anaplasia, and mitoses were numerous [Figure 2a and b]. There was a sharp demarcation between the tumor tissue and the surrounding compressed cerebral parenchyma, which showed gliosis and nerve fiber degeneration [Figure 2c]. Immunohistochemical stains revealed strong positivity for cytokeratin (CK) 7 and CK5/6 [Figure 2d and e], and also immunopositive for human papilloma virus (HPV), which was confirmed by in situ hybridization for HPV [Figure 2f].

![Figure 1: Pre-operative MRI of brain showing a solitary heterogeneous enhancing solid mass at the right temporal-parietal junction with surrounding edema, mass effect, and early uncal herniation (a and b). Immediate post-operative MRI of brain showing post-operative changes in right temporal-parietal area with gross total resection of the lesion (c and d). MRI of brain seven weeks after surgical resection showing no evidence of tumor progression, significantly improved edema around the resection area, and partially entrapped right occipital horn likely from intraventricular adhesive disease (e and f)](image-url)
Postoperative MRI [Figure 1c and d] of her brain showed gross total resection of the lesion. The patient experienced no neurological complications postoperatively and was recovering well at the time of discharge. In April 2016, a positron emission tomography (PET)/CT scan of the patient’s head, neck, chest, abdomen, and pelvis showed no evidence of recurrent or metastatic disease. The patient had a repeat MRI [Figure 1e and f] of her head in April 2016, which showed no evidence of tumor progression and significantly improved edema around the resection area. Clinically, she was back to independent living without any neurological deficits. She was subsequently treated with stereotactic radiosurgery (SRS) to the resection cavity with a dose of 18 Gy to the 50% isodose curve.

In July 2016, the patient had a left-sided focal clonic seizure and an episode of left-sided weakness. An MRI showed a new single metastatic tumor measuring 2.3 × 3.5 cm² noted in the right temporo-parietal area with significant surrounding edema within temporal lobe and extending into right parietal and occipital lobes [Figure 3a-d]. Given her excellent performance status and only solitary recurrence, she underwent resection of this second metastatic lesion in July 2016 with a postoperative MRI that showed successful tumor resection with residual edema causing minimal left midline shift [Figure 3e and f], and another treatment of SRS to the resection cavity in August 2016. Another PET/CT scan of her head, neck, chest, abdomen, and pelvis was obtained; it showed small bilateral lung nodules in the right middle lobe and ligula likely of inflammatory origin but still concerning of metastases. Given the size and the imaging characteristics of the lesions, decision was made not to biopsy the lesion and obtaining repeat imaging in 6 months that reported stable nodules with no signs of progression; therefore these lesions were unlikely to be metastases. Serial repeat MRIs showed no evidence of disease progression and clinically she remained independent without any neurological symptoms. The plan for the patient is continued monitoring symptoms along with repeat MRI every 3 months.

**DISCUSSION**

The incidence of cervical cancer metastasis to the brain has been reported as ranging from 0.4% to 2.3%.\(^{[14]}\)
Recently, there has been an increase in the number of brain metastases from cervical cancer; this is thought to be due to improved treatment of the primary cancer and therefore increased overall survival.\textsuperscript{[2,3]} In our literature review of cervical cancer metastases to the brain, we found 31 case reports describing 39 patients and five case series analyzing 50 patients [Table 1] in addition to four retrospective reviews involving 60 patients [Table 2]. Majority of the patients presented with other systemic metastatic disease along with the brain metastasis. Only a small fraction of patients presented with isolated brain metastasis in the absence of any systemic disease.

**Clinical presentation**

The median age of all the patients found in our literature review was 48 years, ranging from 29 to 87 years. Of the interval times and mean interval times reported by the articles from our literature review, the median interval time was 17.2 months. The interval time varied greatly with some patients diagnosed with brain metastasis at the time of their primary cancer diagnosis, while some experienced much longer intervals even up to 8 years. The patient from our case was a 75-year-old female with a 2-year interval time from primary diagnosis to brain metastasis diagnosis.

Of the reported symptoms of the patients from our literature review, the most frequent presenting symptoms included headache (31%), hemiparesis/hemiplegia/weakness (16%), seizure (11%), and altered mental status/confusion (9%). Slightly more than half of these patients (55%) experienced multiple lesions, while slightly less than half (45%) were found to have solitary lesions. Most of the brain metastases were supratentorial (75%) and were found in all the different lobes, and although less frequent, the most common area of infratentorial lesions was in the cerebellum. In our case, the patient presented in February 2016 with left-sided ataxia, weakness, facial droop, and an episode of confusion; she was found to have a solitary lesion located supratentorially in right tempo-parietal lobe. She then presented again in July 2016 after a left-sided focal clonic seizure and an episode of left-sided weakness with findings of another single metastatic lesion in right tempo-parietal lobe.

Mahmoud-Ahmed et al. noted that most brain metastases from cervical cancer are poorly differentiated and of various histologic types.\textsuperscript{[11]} From the patients found in our literature review, the pathology of the tumors was mostly poorly differentiated (77%) and squamous cell carcinoma (68%). Nasu et al. observed that only 35.7% of patients with intracranial metastases from cervical cancer had advanced-stage (III–IV) disease.\textsuperscript{[16]} That observation is supported by the approximately 60% patients found in our literature review which reported to have either stage I or stage II. Recurrence at extracranial sites occurred in majority of the patients reviewed in the literature (87%), and most commonly reported in the lung/chest (39%), bone (16%), and abdomen/pelvis (16%). The patient from our case had stage III squamous cell carcinoma of the cervix with only two solitary brain lesion.

Positive immunohistochemistry for CK7 is frequently seen with squamous cell carcinoma of the cervix, which the patient from our case report was found to have from initial brain lesion.\textsuperscript{[6]} Additionally, our patient’s initial brain metastasis was determined to be HPV positive, which is not uncommon as over 99% of cervical cancers are positive for high-risk HPV subtypes 16, 18, and 31.\textsuperscript{[17]} HPV has mechanisms of hiding from immune activation, including decreasing the activity of natural killer cells and Langerhans cells, allowing it to maintain a subtle balance between inflammation and tolerance.\textsuperscript{[52]}

**Treatment**

Similar to intracranial metastasis from other cancers, treatment of intracranial metastasis of cervical carcinoma includes surgery, radiation therapy, SRS, chemotherapy, or a combination of these therapies. Several of the patients from our literature review underwent surgical resection (35%), and many of them received whole brain radiation therapy (WBRT; 48%). However, there were many combinations of different therapies for the treatment plans of these patients, highlighting the lack of standard treatment protocol for this disease process. The most common treatment courses consisted of WBRT alone (17%) and surgical excision plus WBRT (13%); however, the best course of treatment is still not clear at this time with several studies showing benefits of certain multimodal treatment plans. Our literature review shows majority of the younger patients were treated with surgical resection; however, surgical resection in patients greater than 70 years is a rare occurrence. In our case, the patient was treated with surgery, followed by SRS to the resection cavity for both the metastatic lesions. No additional recurrences or new neurological symptoms were noted 6 months following her second tumor resection. We chose to treat with surgical resection in combination with SRS and avoided WBRT because of patients’ excellent performance status.

Surgical resection of cervical cancer metastasis to the brain is typically performed in patients with a solitary tumor or multiple adjacent tumors, patients with critically located or life-threatening metastases, or patients with diagnostic uncertainty.\textsuperscript{[22]} Aggressive treatment either with surgery or SRS followed by adjuvant WBRT and possibly chemotheraphy should be strongly considered, especially for young patients, as it has been shown to increase overall survival.\textsuperscript{[21,23]} Postoperative adjuvant radiation therapy has led to increased survival, better neurological status, and lower recurrence of central nervous system lesions than radiation therapy alone.\textsuperscript{[2,7,11]}

Chura et al. examined 12 cases of patients with intracranial metastases from cervical cancer treated...
# Table 1: Case reports and case series of intracranial metastases from cervical cancer

| Study            | Age, years | Presenting symptoms                                      | Tumor number | Tumor location          | Interval time, months | Pathology                  | Stage | Extracranial recurrences | Treatment                      | Outcome/Survival, months |
|------------------|------------|----------------------------------------------------------|--------------|-------------------------|-----------------------|----------------------------|-------|--------------------------|--------------------------------|--------------------------|
| Agrawal et al.   | 49         | Left hemiparesis, headache, vomiting                     | 2            | Right occipital and right parietal | 36                    | Moderately differentiated SCC | IIB   | None                     | Surgical excision              | Uneventful postoperative recovery, improved neurodeficits |
| Amita et al.     | 54         | Decreased right visual fields, ataxia, vomiting, headache| 1            | Left parieto-occipital    | 46                    | Poorly differentiated SCC   | IIA   | None                     | Surgical excision, WBRT        | Asymptomatic and disease free at 6 month follow-up after treatment |
| Branch et al.    | 46         | Seizure                                                  | 1            | Right frontal            | 72                    | Poorly differentiated SCC   | III    | Lung, cervix              | Surgical excision, WBRT        | Without brain recurrence at > 3 years postoperatively, primary disease under control |
| Brown et al.     | 60         | Dysmetria, left homonymous hemianopsia, confusion         | 1            | Right occipital          | 0.5                   | Poorly differentiated ASC   | IB2   | None                     | Surgical excision, SRS, chemo | Neurodeficits resolved, stable after 5 months |
| Buchsbaum et al. | 34         | Headaches, tinnitus                                      | 1            | Right parieto-occipital  | 0                     | Poorly differentiated SCC   | IB    | None                     | Surgical excision, chemo       | Unknown                  |
| Cordeiro et al.  | 60         | None                                                     | 1            | Right parieto-occipital  | 0                     | Poorly differentiated SCC   | IIB   | None                     | Surgical excision              | Unknown                  |
|                  | 31         | Headache, right homonymous hemianopsia                   | 1            | Left occipital           | NP                    | Poorly differentiated SCC   | NP    | Lung                     | Surgical excision, WBRT        | No deficits or return of cancer 5 years postoperatively |
|                  | 31         | Headache, drowsiness, visual deficits, diplopia, ataxia | 1            | Right cerebellum         | 24                    | Poorly differentiated AC    | NP    | Abdomen                  | Surgical excision, WBRT        | Postoperative pneumonia and UTI, died 1 month later due to UTI complications |
| Cormio et al.    | 51         | Headache, confusion, dizziness                           | 1            | Right frontal            | 29                    | SCC                        | IB    | Bilateral pelvic wall, lung, liver | Surgical excision, cisplatin | Died 10 months later without further cerebral involvement |
| Ding et al.      | 39         | Headache                                                 | 1            | Right temporal           | 6                     | Moderately differentiated SCC | IB2   | Spinal cord               | Surgical excision, WBRT        | Unknown, but declining status |
| Erdis et al.     | 67         | Headache                                                 | 1            | Left temporal            | NP                    | SCC                        | IV    | NP                      | WBRT                           | Unknown                  |
| Gaussmann et al. | 36         | Gait disturbances                                        | 1            | Parieto-occipital        | 36                    | Poorly differentiated SCC   | I     | Lung, pleura, bone, skin, mediastinal LNs | Partial surgical excision, WBRT | Spontaneous remission in all other sites 10 years after initial dx |
| Gaze et al.      | 32         | NP                                                       | 1            | Left temporo-parietal    | 60                    | Poorly differentiated SCC   | IIB   | Pelvis                   | Surgical excision, WBRT        | Death 1.5 years after brain met dx from recurrent pelvic and intracranial met |

Contd...
| Study             | Age, years | Presenting symptoms                                                                 | Tumor number | Tumor location         | Interval time, months | Pathology                        | Stage | Extracranial recurrences | Treatment               | Outcome/Survival, months |
|-------------------|------------|-------------------------------------------------------------------------------------|--------------|-------------------------|-----------------------|----------------------------------|-------|--------------------------|-------------------------|--------------------------|
| Gill et al.       | 59         | Left leg pain, decreased strength and ataxia in left arm/leg, left facial paresis, confusion, headache | 1            | Right parietal          | 24                    | Poorly differentiated SCC        | NP    | None                     | Pelvis, bone, multiple LNs, lung, large intestines | 2                        |
| Kumar et al.      | 48         | Headache, left hemiparesis, left facial palsy                                       | Multiple     | Right parietal          | 7                     | AC                              | IIB   | None                     | WBRT, chemo             | Residual facial paresis, but significant regression of lesions 3 months after WBRT 11 |
|                   | 50         | Headache, impaired memory                                                           | 1            | Right occipital         | 36                    | SCC                             | IIB   | Left cervical LN         | Surgical excision, WBRT | Significant resolution brain met; subsequent chemo resulted in complete regression of cerebral LN met 67 |
| Marongiu et al.   | 48         | Right arm focal seizure                                                             | 1            | Left parietal           | 54                    | Poorly differentiated SCC        | NP    | None                     | WBRT, chemo             | 11                      |
|                   | 34         | None                                                                                | 1            | Left frontotemporal     | 18                    | NP                              | NP    | None                     | Surgical excision       | Well at 7-month follow-up |
| Nagar et al.      | 72         | Headache, left hemiplegia                                                          | Multiple     | Bilateral cerebellum and cerebrum, right basal ganglia, thalamus, bilateral peduncle, pons | 9                     | Moderately differentiated adenocarcinoma | IIA   | Omentum                  | Steroids, WBRT          | Condition declined and patient died 2 weeks after WBRT |
| Omari-Alaoui et al.| 48        | Headache, vomiting, cerebellar signs                                               | 1            | Left cerebellum         | 8                     | Undifferentiated SCC             | IB    | Liver, lung, bone        | Surgical excision, WBRT | 8                        |
|                   | 67         | Increased ICP, cerebellar signs                                                    | 3            | Cerebellum              | 9                     | Poorly differentiated SCC        | IIB   | None                     | WBRT                    | Alive 2 months following WBRT |
| Park et al.       | 48         | Headache, dizziness                                                                | Multiple     | Cerebrum and cerebellum | 30                   | Poorly differentiated SCC        | IIB2  | Left SCLN                | Steroids, WBRT          | Neuro symptoms resolved, alive 6 month after WBRT Unknown |
| Peters et al.     | 38         | Seizures, slurred speech, expressive aphasia, right hand weakness                  | 1            | Left fronto-parietal    | NP                    | SCC                             | IIB   | Lung                     | Surgical excision       | Unknown |
| Pyeon et al.      | 44         | Headache, dizziness, ataxia                                                        | 1            | Right frontal 1-left parieto-occipital | 8                     | Poorly differentiated neuro-endocrine + SCC | IIA2  | None                     | WBRT                    | Symptoms resolved, survived without evidence of disease for 7 months 8 years after initial dx without any recurrence |
| Robinson et al.   | 68         | Dizziness, headache, ataxia                                                       | 1            | Right cerebellum        | 24                    | Poorly differentiated SCC        | IIB   | None                     | Surgical excision, WBRT | 8 years after initial dx without any recurrence |

Contd...
| Study                    | Age, years | Presenting symptoms                                                                 | Tumor number | Tumor location                                      | Interval time, months | Pathology          | Stage | Extracranial recurrences | Treatment                                                                 | Outcome/Survival, months |
|-------------------------|------------|-------------------------------------------------------------------------------------|--------------|-----------------------------------------------------|-----------------------|--------------------|-------|-------------------------|----------------------------------------------------------------------------|----------------------------|
| Sato *et al*. [44]      | 50         | Headache, vertigo, amnesia, vomiting, left hemiparesis, left facial paresis          | 1            | Right frontal                                       | 0                     | Poorly differentiated SCC | IIB   | Cervix, liver, lungs, mediastinal LNs | Surgical excision, WBRT, chemo (irinotecan, nedaplatin, cisplatin) SRS          | Palliative care, died 7 months after primary dx |
| Senapati *et al*. [46]  | 45         | Headache, vomiting, left hemiparesis                                               | 1            | Right parietal                                       | NP                    | Poorly differentiated SCC | IB    | Lung                    | Surgical excision, WBRT                                                   | Placed in palliative care after lung metastases |
| Setoodeh *et al*. [46]  | 53         | Aphasia, right hemiparesis                                                          | 1            | Left parietal                                        | 0                     | Poorly differentiated SCC | IVB   | Liver, lung              | Surgical debulking                                                       | Died postoperatively due to multiple cerebral hemorrhages |
| Tajran *et al*. [47]    | 59         | Headache                                                                            | 1            | Right tempo-parietal                                 | 96                    | Well to moderately differentiated AC | IB    | Vagina, lung              | Surgical excision, WBRT                                                   | 4.5                                       |
| Vitorino-Araujo *et al*. [49] | 55     | NP                                                                                  | 1            | Left frontal                                         | NP                    | SCC                 | IIIB  | Scalp, skull             | Surgical excision                                                        | Recovered well with no neuro deficits, continued follow-up |
| Wuntkal *et al*. [50]   | 44         | Headache, vomiting, seizures, vision loss                                           | None         | CSF showed carcinomatous meningitis                  | 0                     | Poorly differentiated ASC | IV    | None                    | Intrathecal methotrexate, WBRT, parenteral dexamethasone, carboplatin      | 5                                         |
| Azimirad *et al*. [51]  | 49         | AMS, resting tremor, rigidity, bradykinesia                                         | 1            | Right frontal extending into internal capsule        | 24                    | Poorly differentiated SCC | IIb/IIa Bladder, vaginal stump, rectum, sigmoid colon, abdominal wall, ureter | None                                                                      | Died few days after Parkinsonism symptoms |
| Gupta *et al*. [22]     | 52         | Left facial twitching/droop, left thumb paresthesia                                 | 1            | Right frontal                                       | 0                     | Poorly differentiated ASC | NP    | Uterus, vagina, bladder | Surgical excision, WBRT, cisplatin                                       | 6                                         |

Contd...
| Study                  | Age, years | Presenting symptoms                                                                                                                                 | Tumor number | Tumor location                                                                 | Interval time, months | Pathology                                | Stage | Extracranial recurrences | Treatment                                                                 | Outcome/Survival, months |
|------------------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------|---------------------------------------------------------------------------------|-----------------------|------------------------------------------|-------|--------------------------|--------------------------------------------------------------------------------|--------------------------|
| Lefkowitz et al.        | 29         | Seizure, right hemiparesis and paresthesias                                                                                                         | 2            | Left frontal and right parietal                                                  | 7                    | Moderately differentiated SCC            | IIIB  | Lung                      | WBRT                                                                        | NP                       |
|                        | 68         | Confusion, speech disturbances, right hemiparesis                                                                                                   | 1            | Left occipital                                                                  | 39                   | Moderately differentiated ASC           | NP    | Bone, lung, vulva            | WBRT                                                                        | NP                       |
|                        | 31         | Headache, diplopia, left CN 6 palsy, left mandibular pain and left facial numbness                                                                  | 1            | Left Meckel's cave extending to clivus and wall of sella                        | 12                   | Poorly differentiated small cell carcinoma | NP    | None                       | Surgical excision, WBRT, doxorubicin, cyclophosphamide, vincristine         | NP                       |
| Ziainia et al.          | 38         | Right hemiballism                                                                                                                                    | 1            | Left cerebral peduncle extending into basal ganglia                             | 4                    | Poorly differentiated SCC               | IIB   | para-aortic LNs            | WBRT                                                                        | 4                        |
| Salvati et al.          | 48         | Right arm focal seizures                                                                                                                           | 1            | Left parietal lobe                                                              | 54                   | Poorly differentiated SCC               | NP    | System disease after tx of brain met | Surgical resection, WBRT, chemo                                             | 11                       |
| Chung et al.            | 33         | Headache                                                                                                                                          | 6            | Included frontal, temporal, occipital lobes, and cerebellum                   | Median: 38 Range: 8.7-127.2 | SmCC IIA                                | SmCC  | None                       | SRS and WBRT                                                               | 1.0                      |
|                        | 47         | Headache, weakness                                                                                                                                  | 14           |                                                                                   |                       | SCC IIA2                                 | SCC   | Lung                       | SRS and WBRT                                                               | 13.8                     |
|                        | 40         | Headache, dizziness                                                                                                                                 | 16           |                                                                                   |                       | SCC IIA2                                 | SCC   | Lung, bone                 | SRS and WBRT                                                               | 4.6                      |
|                        | 47         | Seizure                                                                                                                                           | 4            |                                                                                   |                       | AC IIB                                  | AC    | Lung                       | SRS and WBRT                                                               | 1.2                      |
|                        | 62         | Headache                                                                                                                                          | 1            |                                                                                   |                       | SCC IIB                                 | SCC   | Lung, bone                 | SRS and WBRT                                                               | 10.8                     |
|                        | 79         | Disturbed consciousness                                                                                                                                 | 1            |                                                                                   |                       | SCC I1                                 | SCC   | None                       | SRS                                          | 3.1                      |
|                        | 63         | Weakness                                                                                                                                          | 13           |                                                                                   |                       | NP NP                                   | NP    | LN                         | SRS and WBRT                                                               | 9.3                      |
|                        | 50         | Headache, weakness                                                                                                                                  | 3            |                                                                                   |                       | NP NP                                   | NP    | Abdomen                    | SRS and WBRT                                                               | 5.5                      |
|                        | 47         | Seizure, weakness                                                                                                                                  | 2            |                                                                                   |                       | SmCC NP                                 | SmCC  | Lung, abdomen              | SRS                                          | 9.0                      |
|                        | 52         | Headache                                                                                                                                          | 1            |                                                                                   |                       | SCC IIA                                | SCC   | Lung                       | SRS                                          | 15.9                     |
|                        | 61         | Headache                                                                                                                                         | 6            |                                                                                   |                       | SCC IIA                                | SCC   | Lung, bone                 | SRS                                          | 3.8                      |
|                        | 31         | Seizure                                                                                                                                           | 1            |                                                                                   |                       | SmCC I1                                 | SmCC  | None                       | SRS                                          | 1.2                      |
|                        | 54         | Headache                                                                                                                                         | 6            |                                                                                   |                       | SCC IIB                                 | SCC   | Lung                       | SRS and WBRT                                                               | 4.3                      |
| Study                  | Age, years | Presenting symptoms | Tumor number | Tumor location     | Interval time, months | Pathology | Stage | Extracranial recurrences | Treatment                           | Outcome/Survival, months |
|------------------------|------------|---------------------|--------------|--------------------|-----------------------|-----------|-------|--------------------------|-------------------------------------|--------------------------|
| Chura et al. [10]      | Median: 44.5, Range: 31-58 | Headache, confusion | Multiple | Diffuse            | 16.4                  | SCC       | IB1   | Chest, pelvis            | Steroids, WBRT             | CR, 1.5                  |
|                       |            | Paralysis           | Multiple     | Diffuse            | 85.8                  | SCC       | IB1   | Chest                   | Steroids, WBRT             | CR, 3.9                  |
|                       |            | Confusion           | 1           | Frontal            | 25.4                  | AC        | IB2   | Chest, pelvis           | Steroids, WBRT             | CR, 0.6                  |
|                       |            | Seizures            | 2           | Parietal, occipital| 18.6                  | SCC       | IIB   | Chest, abdomen, pelvis  | Steroids alone              | CR, 0.4                  |
|                       |            | Headache            | 1           | Frontal            | 24.6                  | SCC       | IIB   | Chest, pelvis           | Steroids, WBRT             | CR, 4.4                  |
|                       |            | Headache            | 2           | Parietal           | 96.1                  | AC        | IB1   | Abdomen, pelvis         | Steroids, surgery, WBRT     | CR, 6.2                  |
|                       |            | Seizures            | NP          | Leptomeningeal     | 16.0                  | AC        | IIB   | Chest, bone             | Steroids alone              | CR, 3.3                  |
|                       |            | Headache            | Multiple    | Diffuse            | 16.0                  | AC        | IIA   | None                    | Steroids, WBRT             | PD, 3.0                  |
|                       |            | Paralysis           | 1           | Parietal           | 1.1                   | SCC       | IB1   | Chest, bone             | Steroids, WBRT             | PD, 7.9                  |
|                       |            | Headache            | Multiple    | Diffuse            | 2.9                   | SCC       | IB1   | Chest, abdomen, pelvis, bone | Steroids, WBRT             | PD, 1.1                  |
|                       |            | None                | 1           | Frontal            | 27.9                  | SCC       | IIB   | Abdomen, pelvis, bone   | Steroids alone              | CR, 0.5                  |
| Hwang et al. [23]      | 59         | Headache, left hemiplegia | Multiple | Right cerebellum   | 12.3                  | SCC       | IIB   | Lung, liver             | WBRT                   | PD, 0.3                  |
|                       | 52         | None                | 1           | Left cerebellum    | 19.6                  | ASC       | IIB   | Lung, liver             | Irinotecan, SRS             | Median survival: 5.9      |
|                       | 75         | Headache, aphasia   | 1           | Left temporal      | 51.2                  | SCC       | IIIB  | Lung, SCLN              | Surgical excision, WBRT    | (range: 0.7-19 months)    |
|                       | 47         | Seizure             | Multiple    | Both cerebrum      | 5.4                   | SCC       | IIIA  | SCLN                    | Paclitaxel, CAV, Ommaya reservoir insertion, WBRT | |
|                       | 58         | NP                  | Multiple    | Left frontal       | 83.3                  | SmCC      | NP    | Lung, liver             | SmCC                  | (range: 0.7-19 months)    |
|                       | 44         | Headache, vomiting, RUE weakness | Multiple | Both cerebrum, cerebellum | 3.4                   | SCC       | IVB   | Lung, liver, bone, mediastinal LN | Steroids, WBRT | |
|                       | 50         | NP                  | Multiple    | Both cerebellum, left frontal | 34.1                  | SmCC      | IB    | Lung                    | Etoposide + cisplatin, CAV | |
| Study                     | Age, years | Presenting symptoms                                                                 | Tumor number | Tumor location                                      | Interval time, months | Pathology            | Stage | Extracranial recurrences | Treatment | Outcome/Survival, months |
|--------------------------|------------|-------------------------------------------------------------------------------------|--------------|-----------------------------------------------------|-----------------------|----------------------|-------|--------------------------|-----------|--------------------------|
| Ikeda et al. [24]        | 41         | Headache, headache                                                                  | Multiple     | Both cerebrum, cerebellum, skull                    | 4.9                   | AC                   | IVB    | Mediastinal LN, bone     | WBRT      | 33                       |
|                          | 33         | RUE weakness                                                                        | Multiple     | Both frontal, right cerebellum                      | 15.4                  | AC                   | IVB    | Lung, SCLN, para-aortic LN | WBRT      | 41                       |
|                          | 47         | Seizure, Confusion, dysphagia, left hemiplegia                                      | Multiple     | Both cerebrum                                       | 5.4                   | SCC                  | IIIB   | Pleura, SCLN             | WBRT      | 74                       |
|                          | 74         | Confusion, dysphagia, left hemiplegia                                              | NP           | NP                                                  | 49.0                  | AC                   | NP     | Lung                     | Refused treatment | 47                       |
| Mahmood-Ahmed et al. [31]| 42         | Most experienced headaches                                                          | 2            | Cerebrum in 4 patients, both cerebrum and cerebellum in 2 patients, occurring in all lobes | 0.25                  | ASC                  | IB     | Left cervical LN         | WBRT      | 28                       |
|                          | 46         |                                                                                     | 1            | Cerebrum                                           | 2.5                   | SCC                  | IIB    | LN in 2 patients, lung and ribs in 3 patients after brain met dx | SRS       | 10                       |
|                          | 39         |                                                                                     | 4            | Cerebrum                                           | 75                    | AC                   | IIB    | Surgical resection, WBRT | WBRT      | 75                       |
|                          | 40         |                                                                                     | 15           | Cerebrum                                           | 12                    | ASC                  | IIB    | WBRT                     | WBRT      | 95                       |
|                          | 69         |                                                                                     | 1            | Cerebrum                                           | 0                     | SCC                  | IVB    | WBRT                     | WBRT      | 79                       |
|                          | 42         |                                                                                     | 5            | Cerebrum                                           | 18.5                  | SCC                  | IIB    | WBRT, SRS                | WBRT, SRS  | 30                       |

Interval: time from initial primary diagnosis to brain metastasis; Stage: of cervical cancer; Survival: from diagnosis of brain metastasis; neuro: neurological; AMS: altered mental status; met: metastasis; bilat: bilateral; dx: diagnosis; SmCC: small cell carcinoma; SCC: squamous cell carcinoma; AC: adenocarcinoma; ASC: adenocarcinoma; UTI: urinary tract infection; SCLN: supraclavicular lymph node; LN: lymph node; CAV: cyclophosphamide, doxorubicin, vincristine; CR: complete resolution; PD: progressive disease; SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy; Chemo: chemotherapy; RUE: right upper extremity; NP: not published.
with steroids, WBRT, surgery, or a combination of those therapies. The median survival from diagnosis of brain metastasis was 2.5 months (0.3–7.9 months); improved survival was observed in patients who had surgery and patients who underwent SRS with a median survival of 6.2 months vs. 1.3 months for patients treated with only WBRT ($P = 0.024$). Furthermore, chemotherapy seemed to improve survival with a median of 4.4 months in patients who received chemotherapy after WBRT compared to 0.9 months for patients who did not receive additional treatment after WBRT ($P = 0.016$).[10]

SRS appears to offer effective local tumor control for gynecologic malignancies with a study by Matsunaga et al.[15] reporting a control rate of 96.4% and response rate of 93%, 6 months after SRS treatment. The decision to use SRS instead of the conventional surgical excision plus adjuvant WBRT for the treatment of intracranial cervical cancer metastases should be determined on an individual basis with consideration of tumor size (<3 cm), number, and location, in addition to clinical status and available technology.[11,14] Chung et al. analyzed 13 patients with brain metastases from cervical cancer—4 patients treated with SRS and 9 patients with both SRS and WBRT. The median survival from diagnosis of brain metastasis was 4.6 months for patients treated with SRS and WBRT compared to only 1.2 months for patients treated with SRS alone ($P = 0.012$). SRS with WBRT seemed to improve survival; however, patients with poorer prognosis were more likely to be treated with SRS alone instead of combination therapy. Chung et al.[9] suggested that surgical excision or SRS—depending on location, size, and number of lesions—followed by WBRT appears to be an optimal treatment course. They also encouraged the use of SRS as palliative therapy for patients with the goal of providing relief of their symptoms and maintaining a good quality of life; SRS may be the better option for palliative care compared to WBRT, which requires more scheduled sessions in comparison.[9,33]

Chemotherapy plays a significant role in the treatment of cervical cancer, specifically cisplatin; however, its effects on the outcome of intracranial cervical cancer metastases is still not clear but may be used initially in the setting of multiple lesions.[11] Topotecan has specific activity against cervical cancer and is able to cross the blood–brain barrier, which suggests that topotecan may be one of the best chemotherapeutic medications in the treatment of intracranial metastatic cervical cancer.[16,21] Other treatments for unresectable cerebral metastases, such as selective intra-arterial chemotherapy, hormonal therapy, and reversible blood–brain barrier modifiers have not been shown to have a considerable effect.[11]

**Prognosis**

Although reported incidence of intracranial metastases from cervical cancer is low, autopsy reports have noted that up to 3–10% of cervical cancer patients have brain metastases, which brings to question if and when central nervous system screening should be performed.[6] Brown et al.[7] described a case of brain metastasis after only 2 weeks of being diagnosed with stage IB2 cervical cancer and urged oncology physicians to anticipate this event in order to provide early and comprehensive treatment. However, routine cranial radiological evaluation in the absence of symptoms is not recommended because the incidence of brain metastases from gynecological cancers is quite low, but increased awareness of sentinel symptoms, such as headache, nausea, and vomiting, may help in earlier detection of brain metastasis.[14]

In the early stages of cervical cancer (stage I–IIb), there is a 5-year survival of 65–80% of patients, while there is a 0% 5-year survival with disseminated metastases.[18] Cervical cancer metastasis to the brain carries a poor long-term prognosis with a reported median survival of around 2–5 months[22,9] and the majority of patients not surviving beyond 1 year.[6] Several of the case reports did not report overall survival of their patients. Of the patients from this literature review with reported survival times or median survival times, the mean survival time of these patients was 7 months and the median survival time of these patients was 4.6 months, ranging from immediate postoperative death up to 6.5 years. Four patients were reported alive at follow-up after multiple years—3, 5, 8, and 10 years—after their diagnosis of intracranial cervical cancer metastasis. It has been postulated that long-term survival might be due to prolonged therapeutic effects from different genes responsible for metabolizing chemotherapeutic agents, which has been seen in some patients.[18]

The outcome of patients with intracranial metastases from cervical cancer is influenced by the patient's neurological condition, length of clinical history, age, pathological subtype, number of tumors, and comorbidities; good prognostic factors include age <50 years, single brain metastasis, good performance status, and no extracranial metastases.[11,22]

New research is focusing on identifying molecular characteristics of gynecologic tumors in hopes of improving diagnosis, determining prognosis, and guiding treatment according to potentially targetable biomarkers.[14] Zhao et al.[12] discovered decreased mRNA levels of the positive immune factors OX40L/OX40 and Smad3 and increased mRNA levels of the negative immune factors FoxP3 and CCL22/CCR4 in the local microenvironment in tissue samples from patients with cervical cancer compared to normal cervical tissue. Another study found that expression of KIP20A was linked to poorer survival among patients and may contribute to progression of early-stage (I and II) cervical squamous cancer.[11]

Additionally, signaling activation of the protein kinase mTOR, which is involved in protein synthesis, has been...
| Study                        | n  | Mean age (range), years | Presenting symptoms | Tumor number - N | Tumor location | Mean interval (range), months | Pathology | Stage         | Extracranial recurrences | Treatment | Median survival, months |
|------------------------------|----|-------------------------|---------------------|------------------|---------------|-----------------------------|-----------|---------------|--------------------------|-----------|-------------------------|
| Gressel et al.[21]           | 6  | 52 (47-77)              | Yes - 5 No - 1      | Multiple - 5     | Single - 1    | 42.5 (1-116)               | AC - 1    | I - 1         | Lung - 4                 | WBRT - 4  | 3 (1-22)                |
|                              |    |                         |                     |                  |               |                             | SCC - 3   | II - 1        | Bone - 3                 | Surgery + WBRT - 1 |                        |
|                              |    |                         |                     |                  |               |                             | ASC - 2   | IV - 3        | Liver - 2                |                        |                        |
|                              |    |                         |                     |                  |               |                             | NP        | IV - 6        | H&N - 1                 |                        |                        |
| Kim et al.[26]               | 10 | 43 (22-70)              | NP                  | Multiple - 8     | Single - 2    | 33.1 (0-84-3)             | NP        | I - 1         | NP                       | Surgery - 3 | 8.4 (6.6-10.1)          |
|                              |    |                         |                     |                  |               |                             |           | II - 1        | RT - 10                  |                        |                        |
|                              |    |                         |                     |                  |               |                             |           | III - 2       | Chemo - 7                |                        |                        |
| Menendez et al.[34]          | 2  | 42                      | NP                  | Single - 2       | NP            | NP                          | NP        | NP            | NP                       | Surgery - 1  | 5                       |
|                              |    |                         |                     |                  |               |                             |           |               | SRS - 2                  |                        |                        |
|                              |    |                         |                     |                  |               |                             |           |               | Chemo - 1                |                        |                        |
| Nasu et al.[36]              | 42 | 53 (32-87)              | Yes - 41 No - 1     | Multiple - 28    | Single - 14   | 36 (0-386)                 | AC - 6    | I - 14        | Yes - 35                 | Surgery - 2  | 5                       |
|                              |    |                         |                     |                  |               |                             | SCC - 27  | II - 12       | No - 7                   | Surgery + RT - 5 |                        |
|                              |    |                         |                     |                  |               |                             | ASC - 2   | III - 5       |                           | Surgery + Chemo - 1 |                        |
|                              |    |                         |                     |                  |               |                             | MEC - 1   | IV - 10       |                           | Surgery + RT + Chemo - 2 |                        |
|                              |    |                         |                     |                  |               |                             | SmCC - 4  | Unknown - 1   |                           | RT - 21     |                        |
|                              |    |                         |                     |                  |               |                             | Unknown - 1 |               |                           | WBRT + Chemo - 3  |                        |
|                              |    |                         |                     |                  |               |                             |           |               |                           | None - 6     |                        |

*n: Number of patients; Interval: time from initial primary diagnosis to brain metastasis; Stage: of cervical cancer; Median survival: from diagnosis of brain metastasis; neuro: neurological; met: metastasis; dx: diagnosis; SCC: squamous cell carcinoma; AC: adenocarcinoma; ASC: adenosquamous carcinoma; MEC: mucoepidermoid carcinoma; SmCC: small cell carcinoma; SCLN: supraclavicular lymph node; LN: lymph node; SRS: stereotactic radiosurgery; CT: chemotherapy; WBRT: whole brain radiation therapy; RT: radiotherapy including WBRT and SRS; RUE: right upper extremity; NP: not published
noted in both HPV-negative and HPV-positive cervical cancer tissues and cell lines; mTOR inhibitors have also shown to effectively decrease the activity of mTOR along with remarkably decreasing tumor burden.[14] Li et al.[10] also identified increased levels of the oncoprotein HBXIP in patients with squamous cell carcinoma of the cervix compared to normal cervical epithelial and that high expression of this protein was related to invasive and metastatic disease with overall lower survival rates. A recent study from 2017 described an array of novel genomic and proteomic features among different subtypes of cervical cancers, identified as keratin-low squamous, keratin-high squamous, and adenocarcinoma-rich as well as HPV-negative, with the hope of future development distinct targeted therapies.[1]

CONCLUSIONS

Cervical cancer metastasis to the brain is an infrequent event. According to our literature review, the median age of diagnosis for these patients was 48 years (29–87 years). The median time interval from primary diagnosis to diagnosis of intracranial metastases was 17.2 months with a wide range spanning from simultaneous diagnosis with primary cervical cancer diagnosis up to 8 years after primary cancer diagnosis. The most common presenting symptoms include headache, weakness/hemiplegia/hemiparesis, seizure, and altered mental status/confusion. The majority of patients were found to have multiple lesions that were mostly supratentorially located. The patients most commonly had poorly differentiated squamous cell carcinoma with additional recurrences at other sites—mainly the chest/lungs, bone, and abdomen/pelvis.

There is no standard treatment for this condition, and a various treatment options and combination of treatment options have been utilized such as surgical excision, WBRT, chemotherapy, and SRS. WBRT with or without surgery has been the most frequently used management. However, treatment should be individualized with the goal of providing symptomatic relief and improving quality of life. Aggressive treatment options should be based on patient’s performance status and not age alone. A multimodal treatment plan is highly recommended as the best approach, specifically suggesting the use of SRS or WBRT for solitary brain metastases followed by chemotherapy for systemic disease, the use of surgical resection with WBRT for solitary brain lesions without systemic disease, and the use of SRS or WBRT and steroids followed by chemotherapy for palliative symptomatic relief.[2.9,10,21,25,29,31]

In general, intracranial cervical cancer metastasis carries poor prognosis. Favorable prognostic factors for patients with cervical cancer brain metastases include age <50 years, single brain metastasis, good performance status, and no extracranial metastases.[11,23] Although intracranial metastasis of cervical cancer is a rare phenomenon, the incidence rate is rising, and future efforts to study this disease process through large prospective randomized trials are warranted to better describe the clinical presentation and identify more effective treatment plans in addition to further exploration of specific targeted therapies to aid in the development of improved treatment for these patients.

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There are no conflicts of interest.

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