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Review Article

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 temporo-parietal 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

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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

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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 IIIB 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].

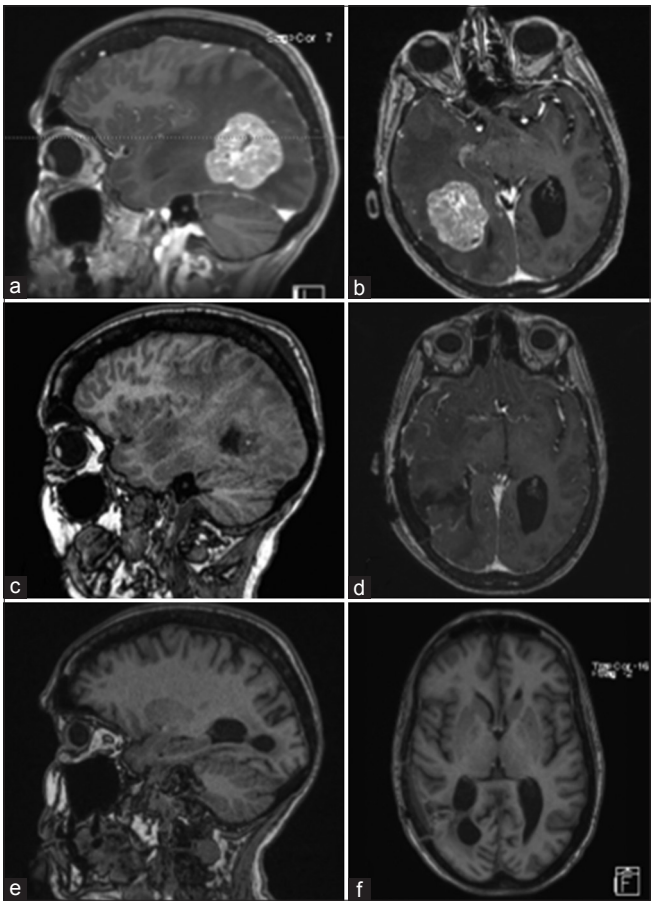

Figure 1: Pre-operative MRI of brain showing a solitary heterogeneously enhancing solid mass at the right temporal-parietal junction with surrounding edema, mass effect, and early uncal herniation (a and b). Immediate post-operative MRI of brain showing post-operative changes in right temporal-parietal 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)

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 cm^2 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]

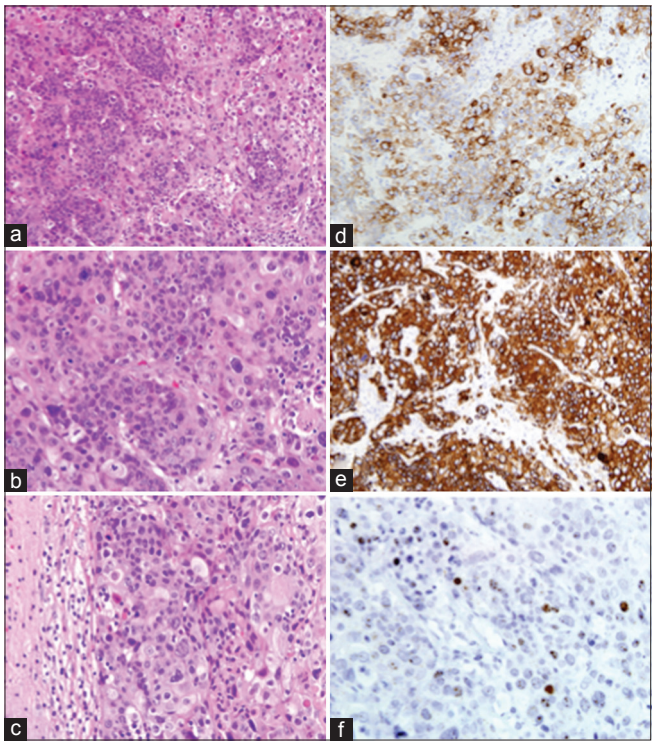

Figure 2: Squamous cell carcinoma of the uterine cervix, metastatic to the brain: marked anaplasia and extensive keratinization of tumor cells. H and E x200 (a) and x400 (b). Note the sharp demarcation between tumor tissue and the surrounding compressed cerebral parenchyma. H and E, x400 (c). Immunohistochemical stains. Tumor cells are strongly positive for CK7 and CK5/6, x400 (d and e). In-situ hybridization for HPV (f)

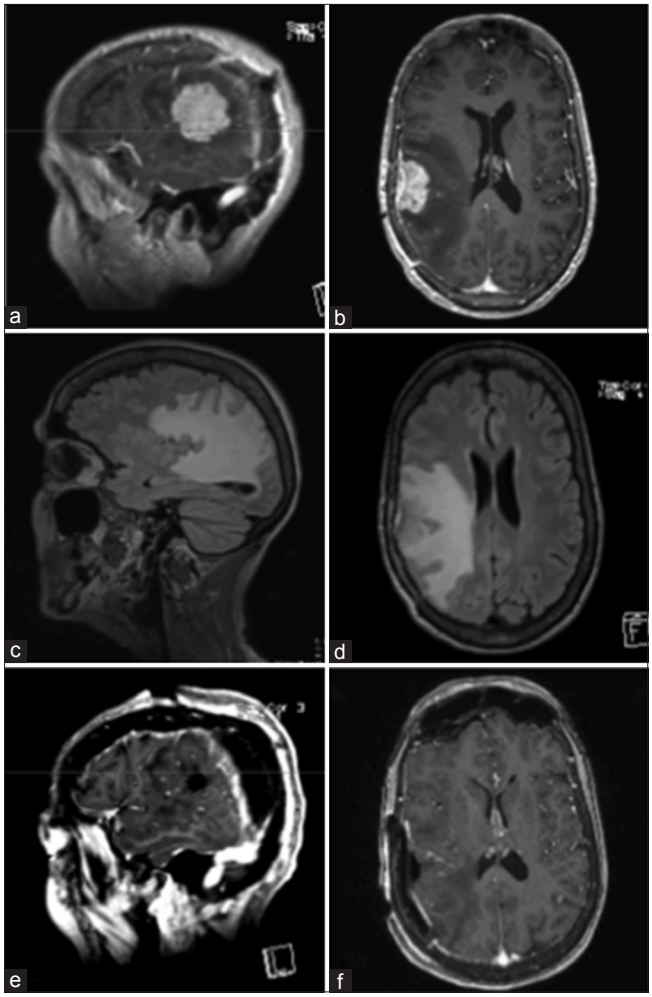

Figure 3: Pre-operative MRI of brain, showing a new enhancing dural based lesion anterior to the prior resection cavity (a-d). Immediate post-operative MRI of brain, demonstrating gross total resection of the lesion (e and f)

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.[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 temporo-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 temporo-parietal lobe.

Mahmoud-Ahmed *et al.* noted that most brain metastases from cervical cancer are poorly differentiated and of various histologic types.[31] 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.[36] 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.[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.[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.[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.[2] Aggressive treatment either with surgery or SRS followed by adjuvant WBRT and possibly chemotherapy should be strongly considered, especially for young patients, as it has been shown to increase overall survival.[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.[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*.[2]	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*.[3]	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*.[6]	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*.[7]	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*.[8]	34	Headaches, tinnitus	1	Right parieto-occipital	0	Poorly differentiated SCC	IB	None	Surgical excision, chemo	Unknown
Cordeiro *et al*.[11]	60	None	1	Right parieto-occipital	0	AC	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*.[12]	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*.[13]	39	Headache	1	Right temporal	6	Moderately differentiated SCC	IB2	Spinal cord	Surgical excision, WBRT	Unknown, but declining status
Erdis *et al*.[15]	67	Headache	1	Left temporal	NP	SCC	IV	NP	WBRT	Unknown
Gaussmann *et al*.[18]	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*.[19]	32	NP	1	Left temporo-parietal	60	Poorly differentiated SCC	IIIB	Pelvis	Surgical excision, WBRT	Death 1.5 years after brain met dx from recurrent pelvic and intracranial met

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Table 1: Contd...

Study	Age, years	Presenting symptoms	Tumor number	Tumor location	Interval time, months	Pathology	Stage	Extracranial recurrences	Treatment	Outcome/Survival, months
Gill *et al*.[20]	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	Pelvis, bone, multiple LNs, lung, large intestines	None	2
Kumar *et al*.[27]	48	Headache, left hemiparesis, left facial palsy	Multiple	Right parietal	7	AC	IIIB	None	WBRT, chemo	Residual facial paresis, but significant regression of lesions 3 months after WBRT
	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 cervical LN met
Marongiu *et al*.[32]	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*.[35]	72	Headache, left hemiplegia	Multiple	Bilat cerebellum and cerebrum, right basal ganglia, thalamus, bilat peduncle, pons	9	Moderately differentiated, adenocarcinoma	IIA	Omentum	Steroids, WBRT	Condition declined and patient died 2 weeks after WBRT
Omari-Alaoui *et al*.[37]	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*.[38]	48	Headache, dizziness	Multiple	Cerebrum and cerebellum	30	Poorly differentiated SCC	IB2	Left SCLN	Steroids, WBRT	Neuro symptoms resolved, alive 6 month after WBRT
Peters *et al*.[39]	38	Seizures, slurred speech, expressive aphasia, right hand weakness	1	Left fronto-parietal	NP	SCC	IIIB	Lung	Surgical excision	Unknown
Pyeon *et al*.[40]	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
Robinson *et al*.[42]	68	Dizziness, headache, ataxia	1	Right cerebellum	24	Poorly differentiated SCC	IIIB	None	Surgical excision, WBRT	8 years after initial dx without any recurrence

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Table 1: 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)	Palliative care, died 7 months after primary dx
			2	Left parietal and cerebellar vermis	4				SRS	
Senapati *et al*.[45]	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
	43	Headache	Multiple	Bilateral hemispheres	0	Poorly differentiated SCC	IVB	Lung, bone	Surgical excision, WBRT, taxol/ cisplatin	Unknown
Tajran *et al*.[47]	59	Headache	1	Right temporo-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*.[5]	49	AMS, resting tremor, rigidity, bradykinesia	1	Right frontal extending into internal capsule	24	Poorly differentiated SCC	IIb/IIIa	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

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Table 1: Contd...

Study	Age, years	Presenting symptoms	Tumor number	Tumor location	Interval time, months	Pathology	Stage	Extracranial recurrences	Treatment	Outcome/Survival, months
Lefkowitz *et al*.[28]	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*.[53]	38	Right hemiballism	1	Left cerebral peduncle extending into basal ganglia	4	Poorly differentiated SCC	IIB	para-aortic LNs	WBRT	4
Salvati *et al*.[43]	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*.[9]	33	Headache	6	Included frontal, temporal, occipital lobes, and cerebellum	Median: 38 Range: 8.7-127.2	SmCC	IIA	None	SRS	1.0
	47	Headache, weakness	14			SCC	IIA	Lung	SRS	13.8
	40	Headache, dizziness	16			SCC	IIA2	Lung	SRS and WBRT	4.6
	47	Seizure	4			AC	IB	Lung	SRS and WBRT	1.2
	62	Headache	1			SCC	IIB	Lung, bone	SRS and WBRT	10.8
	79	Disturbed consciousness	1			SCC	IB1	None	SRS	3.1
	63	Weakness	13			NP	NP	LN	SRS and WBRT	9.3
	50	Headache, weakness	3			NP	NP	Abdomen	SRS and WBRT	5.5
	47	Seizure, weakness	2			SmCC	NP	Lung, abdomen	SRS	9.0
	52	Headache	1			SCC	IIB	Lung	SRS	15.9
	61	Headache	6			SCC	IIIA	Lung, bone	SRS	3.8
	31	Seizure	1			SmCC	IB1	None	SRS	1.2
	54	Headache	6			SCC	IB2	Lung	SRS and WBRT	4.3

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Table 1: Contd...

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	IIIB	Chest, pelvis abdomen	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	IIIA	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
		Headache, confusion	NP	Leptomeningeal	6.4	SCC	IVB	Abdomen, pelvis	Steroids, WBRT	PD, 0.3
Hwang *et al*.[23]	59	Headache, left hemiplegia	Multiple	Right cerebellum	12.3	SCC	IIB	Lung, liver	WBRT	
	52	None	1	Left cerebellum	19.6	ASC	IIB	Lung, liver	Irinotecan, SRS	
	75	Headache, aphasia	1	Left temporal	51.2	SCC	IIIB	Lung, SCLN	Surgical excision, WBRT	Median survival: 5.9
	47	Seizure	Multiple	Both cerebrum	5.4	SCC	IIIA	SCLN	WBRT	
	58	NP	Multiple	Left frontal	83.3	SmCC	NP	Lung, liver	Paclitaxel, CAV, Ommaya reservoir insertion, WBRT	(range: 0.7-19 months)
	44	Headache, vomiting, RUE weakness	Multiple	Both cerebrum, cerebellum	3.4	SCC	IVB	Lung, liver, bone, mediastinal LN	WBRT	
	50	NP	Multiple	Both cerebellum, left frontal	34.1	SmCC	IB	Lung	Etoposide + cisplatin, CAV	

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Table 1: Contd...

Study	Age, years	Presenting symptoms	Tumor number	Tumor location	Interval time, months	Pathology	Stage	Extracranial recurrences	Treatment	Outcome/Survival, months
	41	Headache	Multiple	Both cerebrum, cerebellum, skull	4.9	AC	IVB	Mediastinal LN, bone	WBRT	
	33	RUE weakness	Multiple	Both frontal, right cerebellum	15.4	AC	IVB	Lung, SCLN, para-aortic LN	WBRT	
	47	Seizure	Multiple	Both cerebrum	5.4	SCC	IIIB	Pleura, SCLN	WBRT	
	74	Confusion, dysphagia, left hemiplegia	NP	NP	49.0	AC	NP	Lung	Refused treatment	
Ikeda *et al*.[24]	41	Hemiparesis, headache	1	Right parietal	6.1	Poorly differentiated SCC	IIIB	Peritoneum, pleura, left SCLN	Surgical excision, WBRT	7.5
	41	Hemiparesis	3	Left frontal, temporal	61.8	Undifferentiated	IB1	Right cervical LN	Surgical excision, WBRT	4.1
	66	Vomiting, headache	2	Left temporal, left parietal	28.7	Poorly differentiated AC	IIB	Lung	Surgical excision, WBRT	10.3
	54	Vomiting, headache	2	Right occipital	8.9	Poorly differentiated AC	IIB	Pelvis, bone	WBRT	1.9
	60	Vomiting	4	Both frontal, left parietal	53.5	Poorly differentiated SCC	IIB	Lung, bone	WBRT	1.8
	73	Vomiting	1	Left occipital	14.3	Moderately differentiated SCC	IIB	Bone	WBRT	12.3
	36	Seizure	1	Left frontal	20.5	Poorly differentiated SCC	IB1	Skin	WBRT	2
	59	Seizure	1	Right temporal	33.8	Poorly differentiated SCC	IB2	Left cervical LN	WBRT	22.6
Mahmoud-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	LN in 2 patients, lung and ribs in 3 patients after brain met dx	SRS	22.5
	46		1		2.5	SCC	IIIB		Surgical resection, WBRT	10.5
	39		4		75	AC	IIIB		WBRT	0.5
	40		15		12	ASC	IIB		WBRT	8.25
	69		1		0	SCC	IVB		WBRT	7.25
	42		5		18.5	SCC	IIB		WBRT, SRS	7

*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: adenosquamous carcinoma; 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 2.3 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.*[33] 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.[10,23] 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 2–8 months[2,7,9] 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.[11,23]

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.*[52] 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.[51]

Additionally, signaling activation of the protein kinase mTOR, which is involved in protein synthesis, has been

Table 2: Retrospective chart reviews of intracranial metastases from cervical cancer

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	NP	42.5 (1-116)	AC - 1 SCC - 3 ASC - 2	I - 1 II - 1 IV - 3 Unknown - 1	Lung - 4 Bone - 3 Liver - 2 H&N - 1	WBRT - 4 Surgery + WBRT - 1	3 (1-22)
Kim *et al*.[26]	10	43 (22-70)	NP	Multiple - 8 Single - 2	Supratentorial only - 2 Infratentorial - 8	33.1 (0-84-3)	NP	I - 1 II - 1 III - 2 IV - 6	NP	Surgery - 3 RT - 10 Chemo - 7	8.4 (6.6-10.1)
Menendez *et al*.[34]	2	42	NP	Single - 2	NP	NP	NP	NP	NP	Surgery - 1 SRS - 2 Chemo - 1	5
Nasu *et al*.[36]	42	53 (32-87)	Yes - 41 No - 1	Multiple - 28 Single - 14	NP	36 (0-386)	AC - 6 SCC - 27 ASC - 2 MEC - 1 SmCC - 4 Unknown - 1	I - 14 II - 12 III - 5 IV - 10 Unknown - 1	Yes - 35 No - 7	Surgery - 2 Surgery + RT -5 Surgery + Chemo-1 Surgery + RT + Chemo - 2 RT - 21 WBRT+Chemo - 3 None - 6	5

**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.[4] Li *et al.*[30] 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.[2,9,10,21,23,29,31]

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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Conflicts of interest
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