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Original Article

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

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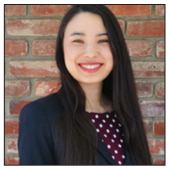

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ABSTRACT

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

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

Results: A total of 89 patients, 25 with IBM and 64 with NIBM, were identified. The time interval between initial diagnosis of cervical cancer and diagnosis of brain lesion was significantly shorter in the IBM group (median 7.5 vs. 20.05 months, and IBM vs. NIBM, respectively; $P = 0.006$). Overall survival from initial diagnosis of cervical cancer was significantly shorter for the IBM group versus the NIBM group (7.63 vs. 26.3 months, respectively; $P = 0.0005$). Data demonstrate a 3.4-fold reduction of median life expectancy to 7.63 months. Survival after diagnosis of brain metastases did not differ between groups (median, IBM 7 months vs. NIBM 4 months, $P = 0.08$).

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

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

INTRODUCTION

Cervical cancer is an aggressive gynecological cancer of the uterine cervix. Tumors may consist of one of many histopathologies, from the more common squamous or adenocarcinomatous tumors to less

common neuroendocrine tumors. While incidence in the US has decreased due to the widespread screening of cervical cytology and adoption of the human papillomavirus vaccine, prevalence remains at a value of roughly 6.8 cases per 100,000 women per year.[6] However, cervical cancer continues to be a leading cause of cancer death in women in less developed countries. Metastases are common, especially in late-stage disease. Among the more frequent sites of distant metastasis are the lungs (21%), para-aortic nodes (11%), and abdominal cavity (8%).[14]

Brain metastasis represents a rather uncommon but known complication. The estimated frequency of brain metastases from cervical cancer seen in the clinical setting ranges from 0.4% to 2%, while autopsy studies have reported brain metastases in 3–10% of cervical cancer patients.[4,10,40] Most patients with cervical cancer brain metastases present at a time of widespread systemic disease and with poor prognosis. Still, other patients may present with isolated brain metastases. To this end, isolated brain metastasis (IBM) from cervical cancer is defined as tissue-confirmed metastasis to the brain without radiographic evidence of metastases to any other region at the time of diagnosis. Given its relative rarity, cervical cancer IBM remains poorly characterized.

It remains unclear if IBM represents a distinct clinical entity from NIBM. Previous reports[11] have suggested that overall tumor burden, and not the development of brain metastasis, is the key determinant in survival for gynecological cancer. Understanding different disease course, should it exist, is critical in therapeutic planning and managing expectations of patients and their families. Toward better understanding, IBM and NIBM in cervical cancer, we conducted a literature review and meta-analysis. Our review of the literature revealed 24 reports of IBM from primary cervical cancer. It remains unclear if patients who present with IBM or the respective primary disease in cervical cancer patients presenting as IBM differs from those observed in patients with non-isolated brain metastases (NIBM) – that is to say, brain metastases in the setting of disease disseminated to other organ systems. We set out to study several parameters including patient characteristics, tumor characteristics, treatments received, and survival between patients with IBM to those with NIBM.

This systematic review serves to determine possibly identify differences by comparing 25 cases of IBM to 64 cases of NIBM. The 25 cases consist of 24 cases found in the literature, and one case that presented to our institution. Although other cases of IBM and NIBM from cervical cancer have been reported, many reports neglect to report key details about the cases and could not be included in this study.

MATERIALS AND METHODS

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

Inclusion criteria

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

Exclusion criteria

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

Data extraction

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

Statistical analysis

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

RESULTS

We identified 238 articles using the selected keywords, and 45 articles matched the topic of cerebral metastases from cervical cancer. Of these articles, 36 articles regarding cervical cancer with brain metastasis published between 1983 and 2018 met the study criteria and included granular patient data with information regarding survival. Twenty-five patients with IBM and 64 patients with NIBM were identified. The mean age in patients with IBM was 48.5 (range ± 11.6 years) and NIBM 49.1 (range ± 11.8 years) was not significantly different ($P = 0.83$). Cancer stage at the time of diagnosis of brain metastasis did not differ significantly between groups (mean stage IBM 2.1, NIBM 2.2, $P = 0.71$). The interval between cervical and brain lesion diagnosis was significantly shorter in the IBM group (7.5 months vs 20.05 months, IBM vs. NIBM, respectively; $P = 0.006$). Comparisons between IBM and NIBM are summarized in Table 1;[1-4,6-10,12-19,21-35] IBM and NIBM patient case details from previous studies are displayed in Table 2[3,5,7-10,19,20,24,26,27,30,33,35,36] and Table 3,[1,4,7,8,10,13,17,18,22,25,26,28,31,32,34,36-39,41,43] respectively.

Histopathology

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

Treatment

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

Survival

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

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

DISCUSSION

Metastasis to the brain from cervical cancer is not common in clinical neurosurgical practice. As such, the possibility of brain metastasis is often not considered until there is evidence of neurological deficit. Based on data from the

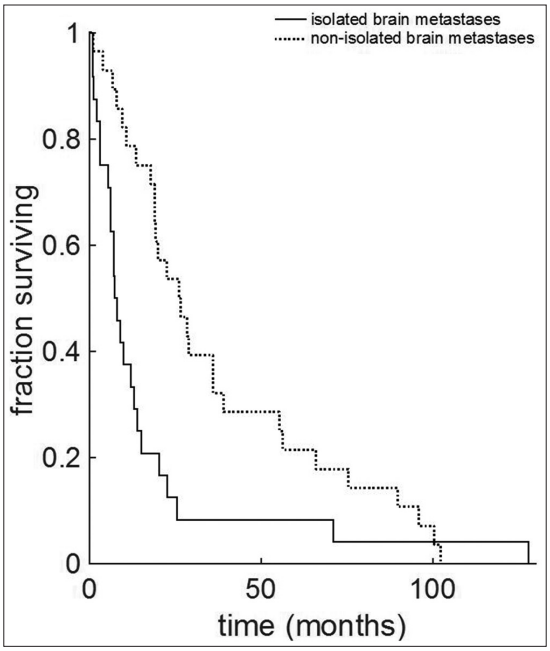

Figure 1: Kaplan–Meier analysis of survival from time of diagnosis of cervical cancer.

Table 1: Comparison of patients with isolated versus non-isolated brain lesions.

	Isolated		Non-isolated		*P*-value
		n		*n*	
Age and disease course					
Age	48.5(±11.6)	25	49.1(±11.8)	57	0.83
Disease interval (median)	7.5 (range 0–60)	22	20.05 (range 0–96.1)	43	**0.0062**
Survival from brain diagnosis (median)	7 (0–100)	16	4 (0.3–96)	37	0.083
Survival from original diagnosis (median)	7.63 (1–128)	13	26.3 (1–102.3)	25	**0.0005**
Presentation of brain metastases					
FND present	13 (62%)	21	25 (45%)	56	0.2742
Cancer stage at the time of diagnosis of brain metastases					
IA	1 (5%)		1 (2%)		0.88
IB	6 (30%)		17 (37%)		0.79
IIA	2 (10%)		2 (4%)		0.74
IIB	6 (30%)		13 (28%)		0.88
IIIA	1 (5%)		3 (6%)		0.75
IIIB	2 (10%)		6 (13%)		0.95
IVA	0 (0%)		0 (0%)		
IVB	2 (10%)		5 (10%)		0.74
Histology		25		58	
Squamous cell carcinoma	14 (60%)		38 (66%)		0.464
Adenosquamous	4 (20%)		3 (5%)		0.231
Neuroendocrine/small cell	4 (20%)		3 (5%)		0.231
Adenocarcinoma	3 (10%)		13 (22%)		0.432
Carcinoid	0 (0%)		1 (2%)		0.66
Distribution					
Solitary	16 (64%)	25	34 (61%)	55	0.95
Multiple	9 (36%)		21 (39%)		0.95
Location		20		35	
Frontal	5 (20%)		10 (29%)		0.97
Parietal	5 (20%)		10 (29%)		0.97
Temporal	0 (0%)		8 (23%)		0.055
Occipital	3 (12%)		4 (11%)		0.97
Cerebellar	7 (28%)		3 (9%)		**0.037**
Treatment of primary cervical cancer		25		56	
Radiation	14 (56%)		30 (54%)		0.97
TAH/RH	8 (32%)		22 (39%)		0.71
CCRT	2 (8%)		7 (13%)		0.82
CTX	7 (28%)		29 (52%)		0.08
Treatment of brain metastases		25		54	
SX+SRS+WBRT	3 (12%)		0 (0%)		0.05
SX+WBRT	2 (8%)		13 (24%)		0.19
SX+SRS	1 (4%)		0 (0%)		0.67
SX only	6 (24%)		3 (6%)		**0.044**
WBRT+SRS	3 (12%)		2 (4%)		0.36
WBRT only	5 (20%)		32 (59%)		**0.0026**
SRS only	5 (20%)		4 (7%)		0.21
CCRT	3 (12%)		1 (2%)		0.17
CTX after surgery/radiation	2 (8%)		5 (9%)		0.8
CTX timing not stated	4 (16%)		3 (2%)		0.27
Total CTX	7 (28%)		9 (16%)		0.38

FND: Focal neurological deficit, SX: Surgery, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiation, CTX: Chemotherapy, CCRT: Concurrent chemoradiotherapy

National Cancer Institute from 2009 to 2013, squamous cell carcinomas comprised 64% of all cervical cancers while adenocarcinomas comprised 15.1% and adenosquamous carcinomas comprised 3.4% of all reported cervical

Table 2: Characteristics of individual patients with isolated brain metastases.

First author	Age	Type of cancer	Stage	Survival from dx of brain metastases	Interval time (mo)	Survival from dx of cervical ca	Initial Tx		Tx for brain metastases		Radiation dose (brain)
Brown 2007[6]	60	Adenosquamous	IB2	5	0.5	5.5	RH, BSO, LND	1	SX/SRS/CTX	4	16 Gy
Sato 2015[7]	50	Squamous	NR	7	0	7	CCRT	4	SX/WBRT/SRS/CTX	4	24 Gy
	42	Adenosquamous	IB	22.5	0.25	22.75	XRT	2	SRS only	2	18 Gy
	46	Squamous	IIIB	10.5	2.5	13	TAH, BSO, XRT	5	WBRT only	2	37.5 Gy
	41	Adenosquamous	IIB	8.25	12	20.25	XRT	2	WBRT only	2	37.5 Gy
	69	Squamous	IVB	7.25	0	7.25	None	nan	WBRT/SRS	2	30 Gy, 9 Gy
Mahmoud-Ahmed 2001[8]	43	Squamous	IIB	7	18.5	25.5	XRT	2	WBRT/SRS	2	35 Gy, 24 Gy
Chura 2007[9]	55	Squamous	IB1	7.9	1.1	9	RH, BSO, LND, CTX	7	WBRT/SRS/CTX	4	40 Gy, 17.5 Gy
Pyeon 2014[10]	44	Large Cell NE	NR	7	8	15	TAH, CTX	7	WBRT	2	NR
	48	Squamous	RPA I	11	60	71	NR	nan	SX/WBRT	4	NR
Marongiu 2012[11]	34	Small Cell NE	RPA I	7	7	14	TAH, CTX, XRT	6	SX only	1	NR
Amita 2005[12]	54	Squamous	IIA	6	6	12	CTX, XRT	4	SX/WBRT/SRS	4	30 Gy, 10 Gy
Robinson 1997[13]	68	Squamous	IIIB	100	28	128	CCRT	4	SX/WBRT/SRS	4	30 Gy, 10 Gy
Gupta 2016[14]	52	Adenocarcinoma	NR	6	0	6	NR	nan	SX only	1	NA
Cormio 1999	49	Squamous	IB	10	29	10	TAH, LND	1	SX only	1	NA
isolated	48	Adenocarcinoma	IIIB1	3	7	3	CTX, XRT	4	WBRT only	2	NA
Kumar isolated	50	Squamous	IIB	7	35	7	XRT	2	SX only	1	NA
	48	Squamous	IB	6	8	6	TAH, XRT, LND	5	SRS only	2	30 Gy, 15 Gy
Omari-Alaoui	67	Squamous	IIB	2	9	2	XRT	2	WBRT only	2	30 Gy
isolated	33	Small cell NE	IIA	1	NA	1	RH+CTx+RTx	5	SRS only	2	18 Gy
	79	Squamous	IB1	3.1	NA	3.1	TAH, XRT	5	SRS only	2	8 Gy
Chung	31	Small Cell NE	IB1	1.2	NA	1.2	TAH, XRT, CTX	6	SRS only	2	25 Gy
Huang	43	Adenosquamous	IIB	nan	24	nan	XRT	2	SX only	2	NA
Cordeiro	31	Adenocarcinoma	IIB	1	24	1	TAH	1	SX/WBRT	4	NA
Current study	50	Squamous	IIB	2	6	8	CTX, XRT	4	SX only	1	NA

dx: Diagnosis, mo: Months, ca: Carcinoma, NE: Neuroendocrine, RPA: Recurrent partioning analysis classification, Tx: Treatment, CCRT: Adjuvant concurrent chemoradiation therapy, XRT: Radiation therapy, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, LND: Lymph node dissection, CTX: Chemotherapy, NR: Not reported, RH: Radical hysterectomy, Gy: Gray, WBRT: Whole brain radiation, Sx: Surgery, SRS: Stereotactic radiosurgery

Table 3: Characteristics of individuals with non-isolated brain metastases.

First author	Age	Type of cancer	Stage	Survival since dx of brain metastases	Interval time (mo)	Survival from time of cervical cancer dx	Initial Tx	Initial tx, coded	Tx for Brain Metastases	Met tx, coded	Radiation dose (brain)
Nagar 2005	72	Adenocarcinoma	IIA	0.5	9	9.5	TAH, BSO, XRT, CTX	5	WBRT	2	30 Gy
Mahmoud 2001	45	Adenocarcinoma	IIIB	0.5	75	75.5	TAH, BSO, XRT, CTX	5	WBRT	2	27 Gy
Erdis 2011	67	Squamous	IVB	nan	–	nan	CTX	3	–	nan	–
	53	Squamous	–	nan	0	nan	–	nan	SX	1	–
Setoodeh 2012	43	Squamous	–	nan	–	nan	–	nan	SX, WBRT, CTX	4	–
Gressel 2015	52.2 (mean 6 pts)	Squamous (3) Adenocarcinoma (3)	I II IV (3) 1 pt not reported	3	–	nan	–	nan	4 XRT 1 SX, XRT, 1 no treatment	4	–
Peters 2010	38	Squamous	IIB	nan	–	nan	CTX, XRT	4	SX	1	–
	47	Squamous	IB1	1.5	16.4	17.9	CTX	3	WBRT	2	37.5 Gy
	30	Squamous	IB1	3.9	85.8	89.7	RH, LND, XRT	5	WBRT	2	37.5 Gy
	40	Adenocarcinoma	IB2	0.6	25.4	26	RH, BSO, LND	1	WBRT	2	33 Gy
	34	Squamous	IIB	0.4	18.6	19	TAH, BSO, CTX	5	None	nan	
	29	Squamous	IIIB	4.4	24.6	29	CTX, RH, BSO, LND, XRT	5	WBRT, SRS	2	38 Gy+17 Gy
	34	Adenosquamous	IB1	6.2	96.1	102.3	RH, LND	1	SX, WBRT	4	30 Gy
	36	Adenocarcinoma	IIB	3.3	16	19.3	CTX	3	None	nan	
	53	Adenocarcinoma	IIIA	3	16	19	CTX	3	WBRT	2	30 Gy
	47	Squamous	IB1	1.1	2.9	4	RH, BSO, LND, CTX, XRT	6	WBRT, SRS	2	40 Gy+17.5 Gy
	48	Squamous	IIB	0.5	27.9	28.4	CTX, XRT	4	None	nan	
Chura 2007	57	Squamous	IVB	0.3	6.4	6.7	CTX	3	WBRT	2	30 Gy
Park 2010	45	Squamous	IB2	6	30	36	TAH, XRT	5	WBRT	2	30 Gy
	59	Squamous	IIB	5.9	12.3	nan	CCRT	4	WBRT	2	–
	52	Adenosquamous	IIB	nan	19.6	nan	CCRT	4	CTX	3	–
	75	Squamous	IIIB	nan	51.2	nan	CCRT	4	SX, WBRT	4	–
	47	Squamous	IIIA	nan	5.4	nan	CCRT	4	WBRT	2	–
	58	Small cell	–	nan	83.3	nan	CCRT	4	CTX	3	–
	44	Squamous	IVB	nan	3.4	nan	CTX	3	WBRT	2	–
	50	Small cell	IB	nan	34.1	nan	RH	1	CTX	3	–
	41	Adenocarcinoma	IVB	nan	4.9	nan	CCRT	4	WBRT	2	–
	33	Adenocarcinoma	IVB	nan	15.4	nan	CTX	3	WBRT	2	–
	47	Squamous	IIIB	nan	5.4	nan	CCRT	4	WBRT	2	–

(Contd...)

Table 3: (*Continued*)

First author	Age	Type of cancer	Stage	Survival since dx of brain metastases	Interval time (mo)	Survival from time of cervical cancer dx	Initial Tx	Initial tx, coded	Tx for Brain Metastases	Met tx, coded	Radiation dose (brain)
Hwang 2013	74	Adenocarcinoma	–	nan	49	nan	RT	2	None	nan	–
	41	Squamous	IIIB	7.5	6.1	13.6	XRT	2	WBRT	2	30 Gy
	41	Undifferentiated carcinoma	IB1	4.1	61.8	65.9	OP*, XRT	5	WBRT	2	35 Gy
	66	Adenocarcinoma	IIB	10.3	28.7	39	XRT	2	WBRT	2	30 Gy
	54	Adenocarcinoma	IIB	1.9	8.9	10.8	OP*	1	WBRT	2	40 Gy
	60	Squamous	IIB	1.8	53.5	55.3	OP*, XRT	2	WBRT	2	40 Gy
	73	Squamous	IIB	12.3	14.3	26.6	OP*	1	WBRT	2	40 Gy
	36	Squamous	IB1	2	20.5	22.5	OP*, XRT	2	WBRT	2	30 Gy
Ikeda 1998	59	Squamous	IB2	22.6	33.8	56.4	OP*, XRT	2	WBRT	2	40 Gy
Tajran 2003	59	Adenocarcinoma	IB	4.5	96	100.5	BSO, LND	1	SX, WBRT	4	45 Gy
Lefkowitz	29	Squamous	IIIB	nan	7	nan	XRT	2	WBRT	2	–
1983	68	Adenosquamous	–	nan	39	nan	XRT	2	WBRT	2	30 Gy
Agrawal 2007	49	Squamous	IIB	nan	36	36	XRT	2	SX	1	–
Branch 2014	46	Squamous	IB	29	60	nan	TAH, CTX, XRT	5	SX, WBRT	4	50 Gy
Gaussman 2006	36	Squamous	IB	96	36	96	TAH, CTX	7	SX, WBRT	4	40 Gy
Ziainia 1999	38	Squamous	–	4	4	8	XRT, CTX	4	WBRT	2	35 Gy
	47	Squamous	IIA	13.8	–	nan	RH, CTX, XRT	66	SRS	2	12 Gy
	40	Squamous	IA2	4.6	–	nan	TAH, CTX, XRT	6	SRS, WBRT*	2	10 Gy
	47	Adenocarcinoma	IB	1.2	–	nan	TAH, CTX, XRT	6	SRS, WBRT*	2	9 Gy
	62	Squamous	IIB	10.8	–	nan	TAH, CTX, XRT	6	SRS, WBRT*	2	9 Gy
	63	–	–	9.3	–	nan	CTX, XRT	4	SRS, WBRT*	2	14 Gy
	50	–	–	5.5	–	nan	TAH, CTX, XRT	6	SRS, WBRT*	2	15Gy
	47	Small cell	–	9	–	nan	TAH, CTX, XRT	6	SRS	2	16 Gy
	52	Squamous	IIB	15.9	–	nan	RH, CTX, XRT	6	SRS	2	17 Gy
	61	Squamous	IIIA	3.8	–	nan	CTX, XRT	4	SRS	2	16 Gy
Chung 2013	54	Squamous	IB2	4.3	–	nan	TAH, CTX, XRT	6	SRS, WBRT*	2	10 Gy
Siedel 1988	37	Carcinoid	IB	0.66	48	nan	TAH, CTX	7	WBRT	2	27 Gy
Tenjarla 2014	45	Squamous	–	1	0	1	None	nan	WBRT	2	30 Gy
Rhiem 2007	40	Squamous	IB1	2	12	20	TAH, XRT, CTX	6	WBRT	2	–

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

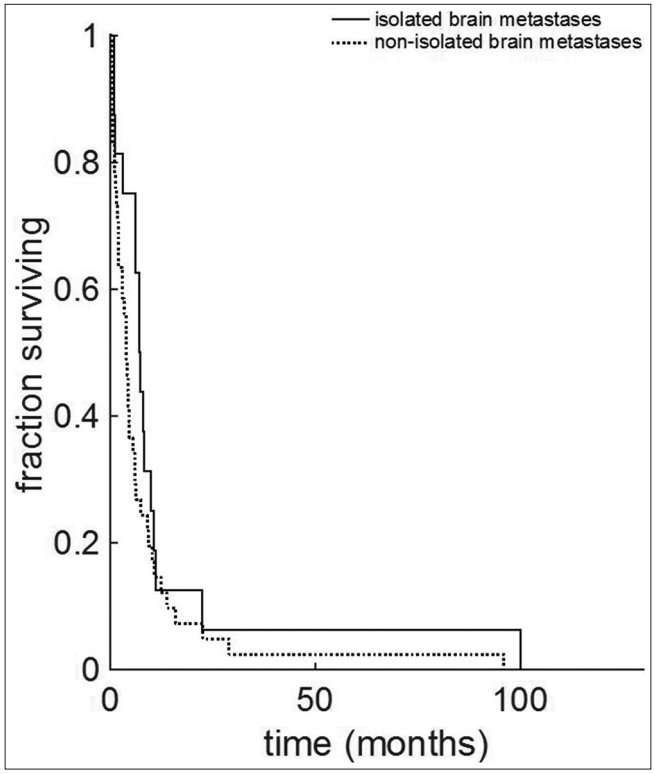

Figure 2: Kaplan–Meier analysis of survival from time of diagnosis of brain metastases.

Table 4: Treatment subgroup analysis.

	IBM	NIBM	*P*-value
Survival since diagnosis			
Surgery	5.5 (1–10)	26.6 (10.8–102.3)	**0.035***
Radiation	20.25 (2–25.5)	37.5 (13.6–56.4)	0.082
Survival since metastasis			
Radiation	6.5 (1–22.5)	4 (0.3–22.6)	0.38

cancers.[19] Our own data reflect this distribution, with squamous cell carcinoma being the most common in both IBM (60%) and NIBM (66%).

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

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

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

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

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

metastases from renal cell carcinoma.[2] Future studies may investigate whether this is true in brain metastases from cervical cancer as well. Future studies may also examine which patients are most likely to benefit from specific brain metastases treatments from specific treatments. A scoring system such as the Score Index for Stereotactic Radiosurgery for Brain Metastases may be used to determine who is most likely to benefit from SRS based on factors including age, number of lesion, and largest lesion volume.[42] Future studies may evaluate whether this scoring system can be used in patients with cervical brain metastases for a better prediction of prognosis.

CONCLUSIONS

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

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTAL TABLE

Supplemental Table 1: Temporal Analysis.

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