



Case series

Treatment patterns and outcomes among women with brain metastases from gynecologic malignancies



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ABSTRACT

Background: Brain metastasis secondary to gynecologic malignancy is rare and has no definitive management guidelines. In this descriptive study, we aimed to identify prognostic factors and treatments that may be associated with longer overall survival.

Methods: Patients with brain metastases from gynecologic malignancies were identified between 2004 and 2019 at two institutions. Descriptive statistics were performed using N (%) and median (interquartile range). Univariate cox proportional hazards regression was performed to evaluate the effect of different factors on overall survival.

Results: 32 patients presented with brain metastasis from gynecologic primaries (ovarian/fallopian tube/primary peritoneal n = 14, uterine n = 11, cervical n = 7). Median age of initial cancer diagnosis was 61 (34–79). At initial cancer diagnosis 83% of patients were Stage III/IV and underwent surgery (66%), chemotherapy (100%), and/or pelvic radiation (33%). Median time from initial cancer diagnosis to brain metastasis was 18 months. Treatment of brain metastasis with surgery and radiation compared to stereotactic radiosurgery or whole brain radiation therapy alone revealed a trend toward longer overall survival (p = 0.07). Time from initial cancer diagnosis to brain metastasis was associated with longer overall survival with each one-month increase from initial cancer diagnosis associated with a 7% reduction in risk of death (HR 0.93, 95% CI = 0.89–0.97, p = 0.01). Initial cancer treatment, stage, histology, and number of brain lesions did not affect overall survival.

Conclusions: Patients with brain metastasis secondary to gynecologic malignancies with the longest overall survival had the greatest lag time between initial cancer diagnosis and brain metastasis. Brain metastasis treated with surgery and radiation was associated with longer overall survival.

1. Introduction

Brain metastasis from gynecologic malignancies is rare and carries a poor prognosis. Loco-regional spread occurs in the majority of metastatic cases from gynecologic malignancies, with distant spread being less common. Metastasis from distant organs typically reach the brain via hematogenous spread. Tumor cells are thought to cross the blood brain barrier through disruption or ischemia of the endothelial cells lining the central nervous system thereby causing increased vascular

permeability (Stewart et al., 1987). Gynecologic cancers with metastasis to the brain have a reported estimated incidence of <2% in ovarian cancer, 0.4–1.2% in cervical cancer, and 0.3–0.9% in endometrial cancer (Kim et al., 2017).

Although brain metastasis from breast, lung, and colorectal cancers have been widely studied, metastasis to the brain from gynecologic malignancies remains poorly understood. Despite improved systemic management of ovarian, endometrial, and cervical cancers, there remain few guidelines on how to best manage these patients once brain

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metastasis is identified. Current treatment options include surgical resection and radiotherapy via whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS). WBRT is typically used for palliative measures in patients with multiple brain metastases who are not surgical candidates or have short life expectancy (Brown et al., 2018). Stereotactic radiosurgery utilizes three-dimensional coordinates to deliver precisely-targeted radiation to small tumors of the brain in fewer high-dose treatments than traditional therapy, which can help preserve healthy tissue. Stereotactic radiosurgery may be the preferred method among patients whose tumor is hard to reach or close to important anatomic regions (Fanous et al., 2019). In this descriptive study, we aim to identify prognostic factors and treatments that may be associated with longer overall survival among women with brain metastasis from gynecologic cancers.

2. Methods

This is a retrospective cohort study approved by the Institutional Review Board at two affiliated institutions, Weill Cornell Medicine and Brooklyn Methodist Hospital, in New York City. Patients with brain metastasis from gynecologic malignancies were identified between these two institutions between 2004 and 2019. Patients were excluded if treatment records or follow up data was unavailable. Data was collected retrospectively from electronic medical records. Clinical variables included primary malignancy (ovarian, uterine, or cervical), stage at initial cancer diagnosis, histologic type, initial cancer treatment, presenting symptom at time of brain metastasis, location and size of brain metastases, and treatment of brain metastasis. Overall survival was stratified based on the treatment of brain metastasis. Treatment modalities included WBRT alone, SRS alone, surgery alone, WBRT and surgery, SRS and surgery, and combined WBRT, SRS, and surgery. Treatment of brain metastasis was decided upon by the individual physician. Surgical resection involved craniotomy performed by neurosurgery. Radiation therapy involved either WBRT or SRS. If WBRT was used, the most common regimen was 30 Gy given in 10 fractions. Stereotactic treatments were given either in a single dose (SRS) or in 3–5 fractions (stereotactic body radiation therapy). Stereotactic body radiation therapy doses varied based on the size and location of the brain metastasis but common regimens included 25 Gy in 5 fractions or 24 Gy in 3 fractions.

Descriptive statistics were utilized to describe the cohort of patients using N (%) and median [interquartile range] for categorical and continuous variables, respectively. Overall survival was calculated from initial cancer diagnosis to date of death as well as from diagnosis of brain metastasis to date of death. Univariate cox proportional hazards regression was performed to evaluate the effect of different prognostic factors on overall survival from initial cancer diagnosis and from diagnosis of brain metastasis. Survival rates were estimated by Kaplan-Meier analysis. All p-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R Version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Because of the small sample size in this pilot study, all results are considered hypothesis-generating and for exploratory purposes.

3. Results

Thirty-two patients with brain metastasis from primary gynecologic malignancies were identified. The median age at diagnosis of initial cancer was 61 years (range 34–79). Initial cancer diagnosis included 14 ovarian/fallopian tube/primary peritoneal, 11 uterine, and 7 cervical cancers. The majority of patients (83%, 24/29) were stage III/IV at time of initial cancer diagnosis. The most common histologic type was carcinoma (77%, 24/31), followed by sarcoma (13%, 4/31), and squamous cell carcinoma (10%, 3/31) (Table 1).

Prior to presentation of brain metastasis, 66% (20/30) of patients underwent surgical management of the primary malignancy. One

Table 1
Characteristics of patients with Brain Metastasis from gynecologic malignancies.

Characteristics of Gynecologic Oncology patients with brain metastases	
Characteristic	Median (range) or Proportion (%)
Age	61 (34–79)
Stage	
I	3/29 (10%)
II	2/29 (7%)
III	8/29 (28%)
IV	16/29 (55%)
Histologic type	
Carcinoma	24/31 (77%)
Sarcoma	4/31 (13%)
Squamous Cell Carcinoma	3/31 (10%)
Location*	
Parietal Lobe	15
Frontal Lobe	10
Cerebellum	12
Occiput	9
Temporal Lobe	9
Other**	22
Presenting Symptom*	
Upper and/or lower extremity weakness/ numbness	24
Headaches	9
Seizures	5
Altered Mental Status	7
Facial Weakness	1
Ataxia	2
Hypertension	2
Abdominal Pain	2
Other***	5
Time to development of brain metastases	
Diagnosis within 1 year	16/31 (52%)
Diagnosis >2 years	15/31 (48%)
Number of Brain Metastases	
Single	11/32 (34%)
Multiple	21/32 (66%)

* Patients often presented with brain metastases in multiple locations and more than one presenting symptom therefore proportions were not calculated for these categories.

** Locations of brain metastases in <2 patients, including temporal, midbrain, pons, pontomedullary junction, thalamus, postcentral gyrus, ventricles, and trigeminal nerve.

*** Presenting symptoms also included nausea, dysarthria, bone pain and dizziness.

hundred percent of patients (30/30) received either neoadjuvant or adjuvant chemotherapy. Thirty-three percent of patients (10/30) received pelvic radiation in addition to surgery and/or chemotherapy. Twenty percent of patients (6/30) received chemotherapy alone. Five patients in our cohort received targeted therapy. One received a PARP inhibitor, two received a monoclonal antibody inhibiting angiogenesis (bevacizumab), and two received a monoclonal antibody inhibiting immune regulation (pembrolizumab).

The median time from initial cancer diagnosis to the diagnosis of brain metastasis was 18 months (range 0–97 months). The most common presenting symptoms at time of brain metastasis diagnosis were extremity weakness and/or numbness (78%) and headaches (28%). 66% (21/32) of patients presented with multiple brain metastases. Common locations for metastases were the parietal lobe (46.9%), frontal lobe (31.2%), or cerebellum (38%). Median size of brain metastasis was 2.7 cm (range < 1.0 to 4.3 cm).

Surgical resection was most often combined with subsequent WBRT and/or SRS. Thirty-three percent of patients were treated with combined WBRT and surgery (10/30), 7% with SRS and surgery (2/30), and 7% with SRS, WBRT, and surgery (2/30). Thirty percent of patients were treated with SRS alone (9/30), 20% with WBRT alone (6/30), and 3% with surgery alone (1/30) (Table 2).

The median follow-up period for all patients was four months (range

Table 2
Treatment of Brain Metastasis.

Treatment of Brain Metastasis	
Whole brain radiation therapy alone	6/30 (20%)
Whole brain radiation therapy + surgery	10/30 (33%)
Stereotactic radiosurgery alone	9/30 (30%)
Stereotactic radiosurgery + surgery	2/30 (7%)
Surgery alone	1/30 (3%)
Whole brain radiation therapy, stereotactic radiosurgery, + surgery	2/30 (7%)

12-month Overall Survival from Diagnosis of Brain metastasis	
WHOLE brain radiation therapy alone	40.0% (95% CI = 13.7–100%)
Stereotactic radiosurgery alone	55.6% (95% CI = 23.1–100%)
Any radiation + surgery	83.3% (95% CI = 64.7–100%)

0–92 months). This relatively short follow up period is likely a reflection of patients who were recently diagnosed as well as patients who died shortly after treatment. Median overall survival from initial cancer diagnosis was 31.7 months (95% CI = 29.3 months, upper limit not estimable) while the median overall survival from diagnosis of brain metastasis to death was 16.2 months (95% CI = 7.6 months, upper limit not estimable). Stage at initial diagnosis, initial cancer treatment with chemotherapy, surgery, and/or radiation, histology type (sarcoma versus carcinoma) and number of brain metastasis (multiple versus single) did not have an effect on overall survival from initial cancer diagnosis ($p = 0.84$; $p = 0.09$; $p = 0.65$; $p = 0.97$, respectively) or from diagnosis of brain metastasis ($p = 0.73$; $p = 0.61$; $p = 0.77$; $p = 0.55$), respectively). However, all Stage IV patients ($n = 4$) had an overall survival from initial cancer diagnosis of 1 year or less.

A trend towards longer median overall survival from diagnosis of brain metastasis was found among patients treated by SRS alone (95.4 months, 95% CI = 2.40 months, upper limit not estimable, $p = 0.14$) as compared to WBRT alone (10.5 months, 95% CI = 2.13 months, upper limit not estimable, $p = 0.14$). A similar non-statistically significant trend in overall survival at one year was identified from diagnosis of brain metastasis among patients who were treated with any radiation plus surgery (83.3%) as compared to SRS alone (55.6%) and WBRT alone (40.0%) ($p = 0.14$ by log-rank test) (Table 2). Treatment with any radiation plus surgery compared to SRS or WBRT alone was associated with longer overall survival from diagnosis of brain metastasis ($p = 0.07$) (Fig. 1a). Treatment with WBRT plus surgery demonstrated a trend toward longer overall survival from diagnosis of brain metastasis as compared to WBRT alone ($p = 0.09$) (Fig. 1b). Duration of time from initial cancer diagnosis to brain metastasis was associated with longer overall survival from diagnosis of initial cancer, with every one-month increment demonstrating a 7% reduction in risk of death (HR 0.93, 95% CI = 0.89–0.97, $p = 0.01$).

4. Discussion

We sought to investigate prognostic factors that led to longer overall survival in patients with brain metastasis from gynecologic malignancies. The most significant finding was related to the length of time between diagnosis of primary cancer and diagnosis of brain metastasis. The longer the time from initial cancer diagnosis to brain metastasis, the longer overall survival with each month demonstrating a 7% reduction in risk of death. This finding was consistent across all types of gynecologic malignancies and histologies in our cohort and has been observed in non-gynecologic malignancies as well. Other factors that may influence outcomes are stage and histology of primary malignancy (McMeekin et al., 2001; Teckie et al., 2013). In our cohort, stage and histology did not show a statistically significant difference in overall survival. However, it was observed that patients who had the shortest

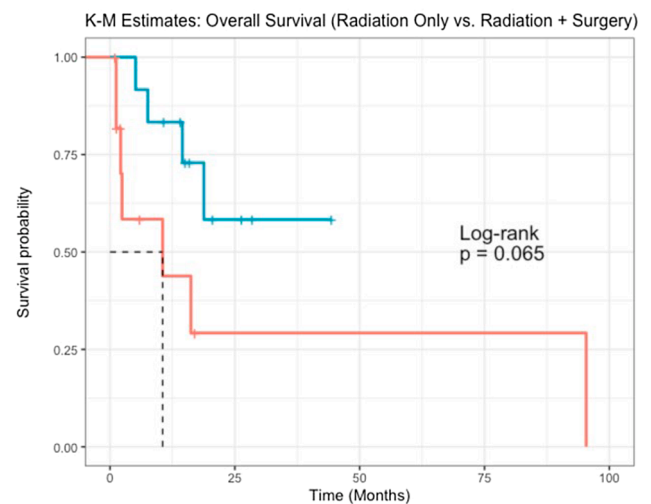


Fig. 1a. Kaplan Meier curve for Overall Survival from Diagnosis of Brain Metastasis for radiation alone (whole brain radiation therapy or stereotactic radiosurgery) versus Radiation + surgery. Treatment with any radiation plus surgery compared to stereotactic radiosurgery or whole brain radiation therapy alone was associated with longer overall survival from diagnosis of brain metastasis ($p = 0.07$). — Radiation alone (whole brain radiation therapy or stereotactic radiosurgery) [red]. — Radiation + surgery [green]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

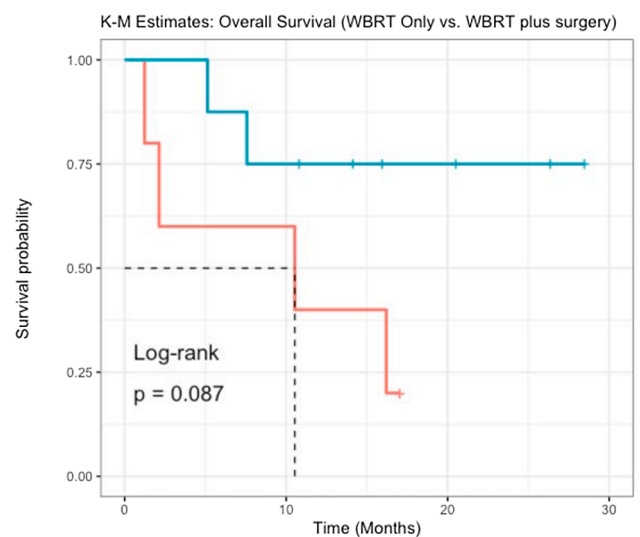


Fig. 1b. Kaplan Meier curve for Overall Survival from Diagnosis of Brain Metastasis for whole brain radiation therapy alone versus whole brain radiation therapy + surgery. Treatment with whole brain radiation therapy plus surgery demonstrated a trend toward longer overall survival from diagnosis of brain metastasis as compared to whole brain radiation therapy alone ($p = 0.09$). — whole brain radiation therapy alone [red]. — whole brain radiation therapy + surgery [green]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

overall survival from initial cancer diagnosis (1 year or less) were initially diagnosed with advanced stage cancer. Also, all of these patients developed brain metastasis within one year from time of initial cancer diagnosis, highlighting the importance of addressing neurologic symptoms in patients with advanced disease. Additional studies have reported that single brain metastases are associated with longer overall survival (McMeekin et al., 2001; Marchetti et al., 2016). In our cohort, we did not find that single versus multiple brain metastasis had any

impact on length of overall survival by either definition.

Of the five patients with the longest overall survival from initial cancer diagnosis (>7 years), 5/5 had ovarian cancer (serous carcinoma = 3, clear cell carcinoma = 1, carcinosarcoma = 1). All five patients underwent initial debulking (80% received optimal debulking) and received adjuvant chemotherapy. 40% (2/5) of these patients received adjuvant bevacizumab, which has been used in brain tumors such as glioblastoma multiforme. Bevacizumab, along with other systemic monoclonal antibodies that cross the blood brain barrier, have shown previously shown promise in treatment of brain metastasis and may account for longer survival (Lampson, 2011). 20% (1/5) received pembrolizumab, a monoclonal antibody causing immune checkpoint inhibition. Previous studies have shown that patients treated with pembrolizumab for brain metastasis in melanoma or non-small-cell lung cancer have demonstrated a favorable response (Goldberg et al., 2016). More studies are required to evaluate the role of immunotherapy among patients with gynecologic malignancies and brain metastasis.

Additional newer targeted therapies may also play a role in longer survival. In our cohort, the patient who lived the longest (> than 100 months) received a poly adenosine diphosphate ribose polymerase (PARP) inhibitor both with adjunctive chemotherapy and after surgery and radiation of brain metastasis. PARP inhibitors have been used with cytotoxic therapies in treatment of resistant glioblastomas. In these cases, resistance likely arises from alterations in deoxyribonucleic acid (DNA) damage response pathways. PARP inhibitors act on these DNA repair mechanisms in order to promote the death of cancer cells and allow normal cells with intact DNA repair mechanisms to survive (Tentori and Graziani, 2005). PARP inhibitors have also independently been shown to lead to increased survival in ovarian cancer.

We also evaluated the type of treatment utilized for brain metastasis to determine association with longer overall survival. Treatment approaches include surgical resection with craniotomy, WBRT, and newer techniques such as SRS. SRS alone has proved to be a safe and effective method for treating brain metastasis from gynecologic malignancies (Monaco et al., 2008). In our cohort of patients, SRS alone revealed a trend towards longer median overall survival as compared to WBRT alone. It is possible that patients who received WBRT had worse disease prior to treatment and this was the major driver for worse survival. However, among this cohort, factors such as Stage, histology and number of brain lesions were similar, suggesting that extent of disease alone may not be the only driver of longer survival. Some studies have found that multimodal therapy with radiation and surgery leads to longer survival (Uccella et al., 2016; Niu et al., 2013; Gilani et al., 2016). In a case series by Kim et al of 20 patients with brain metastasis from gynecologic malignancies, 11 were treated with SRS alone, six with surgery plus WBRT, and three with WBRT alone. Surgery plus WBRT was found to be significantly associated with longer progression free survival than SRS alone (Kim et al., 2017). Our study revealed similar findings with combined WBRT and surgery leading to longer overall survival from diagnosis of brain metastasis. Additionally, among the patients who lived the longest and received multimodal therapy (3/5), radiation followed surgical excision by four months or less. In two of these patients, radiation was completed within the first two months. This highlights the importance of timing between surgical resection and radiation. Although data on time to initiation of radiation after resection of brain metastasis is rare, there is evidence that longer time to initiation is associated with increased local failure and therefore some experts suggest radiation initiation within 30 days of resection (Yusuf et al., 2018). Among the patients that lived the shortest (3 months or less), none underwent surgical resection.

Our study was limited by the small sample size, making it difficult to demonstrate statistical significance across cohorts, but given the rarity of brain metastasis in gynecologic malignancies, we were able to identify important trends that are hypothesis generating and for exploratory purposes. Additionally, this was a retrospective descriptive study with data collected over a long period of time making some clinical data

unavailable for review. Future research with larger sample size would be required to confirm clinical prognostic factors and clarify these relationships in this cohort for specific gynecologic malignancies. Strengths of our study include a large sample size of patients who were derived from two large metropolitan hospitals over a wide study period and who utilized newer targeted therapies as well as multimodal approaches.

Brain metastasis from gynecologic malignancies are uncommon with limited reports in current literature and minimal management guidelines driving therapy at this time. We found that greater length of time from diagnosis of primary cancer to brain metastasis was significantly associated with longer overall survival from initial cancer diagnosis among ovarian, endometrial, and cervical cancers within our cohort. Additionally, treatment with multimodal therapy combining surgical resection and radiation was associated with longer overall survival from diagnosis of brain metastasis among all malignancies. Future studies with larger sample sizes and prospective trials are needed to better understand optimal treatment strategies.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Melissa Frey has research support by Invitae. Kevin Holcomb serves as a consultant for Johnson and Johnson and receives research support from Fujirebio Diagnostics. None of the remaining authors have a conflict of interest to disclose.

Author contribution section

Kristen Cagino helped with conceptualization, data curation, formal analysis, and manuscript writing.

Ryan Kahn helped with data curation, formal analysis and manuscript writing.

Susan Pannullo helped with project administration and manuscript review and editing.

Hani Ashamalla helped with conceptualization, project administration, and manuscript review and editing.

Susie Chan helped with data curation, formal analysis, and manuscript writing.

Onyinye Balogun helped with project administration and manuscript review and editing.

Charlene Thomas helped with formal analysis and manuscript writing.

Paul J. Christos helped with formal analysis and manuscript writing, review, and editing.

Kevin Holcomb helped with project administration and manuscript review and editing.

Melissa K. Frey helped with project administration and manuscript review and editing.

Eloise Chapman-Davis helped with conceptualization, supervision, project administration, formal analysis and manuscript writing, review, and editing.

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