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Central nervous system metastasis in gynecologic cancer: Symptom management, prognosis and palliative management strategies

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HIGHLIGHTS

- CNS metastases are rare in gynecologic cancers; this work evaluates prognostic indices which have performed well in other solid tumors.
- Provides a framework for workup and treatment in gynecologic cancer patients who develop CNS metastases
- Thorough discussion summarizing the role of medical, surgical and radiotherapy interventions for gynecologic cancer patients with CNS metastases

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ABSTRACT

Introduction. CNS metastasis (CNSmet) with gynecologic malignancy (GM) is associated with poor prognosis and symptom burden. Two prognostic indices, the recursive partitioning analysis (RPA) and graded prognostic assessment (GPA), used in other solid tumors to guide intervention options were evaluated among GM patients.

Methods. Retrospective chart review was performed to identify patients with primary GM diagnosed with CNSmet from 2005–2014. RPA and GPA were applied and evaluated for goodness of fit. Long-term survivors (LTS) were those with survival time from CNSmet ≥9 months.

Results. 35 patients were identified with median age of 62 years (range, 41–78). The majority had ovarian cancer (54%). Median survival was 4.5 months (0.1–25.9), and median time from initial diagnosis was 2.6 years (0–19.6). Presenting symptoms varied but headache (57%) and altered mental status (23%) were most common. 37% had a solitary CNS lesion, 31% had 2–8, and 31% >8. 57% were treated with WBRT, 14% with stereotactic radiosurgery (SRS), and 20% with combinations of treatments, and 2 elected for hospice. 27% (9/33) of the patients were LTS.

The GPA was not significantly associated with patient outcome ($p = 0.46$). The RPA predicted time to death ($p = .0010$).

Conclusion. Prognostic indices used to guide therapeutic interventions perform poorly in GM. Detection and aggressive symptom management are critical in maintaining QOL. Multidisciplinary consultation is critical to optimize outcomes and symptom control.

Introduction

Brain metastases due to gynecologic malignancies are rare, although the incidence is increasing, particularly in ovarian cancer [1]. Metastases from ovarian cancer are the most prevalent with estimates ranging from 0.5–3%, and the cumulative incidence of brain metastasis from all gynecologic cancers approximates 1% [2,3]. Due to low incidence, there is no indicated screening program in this population, and the majority presents symptomatically [4,5]. Symptoms vary widely, from mild cognitive impairment and subtle visual changes to seizures and severely altered mental status [6]. These patients can be clinically challenging to manage, as CNS treatment selection is related to prognosis. Prognosis can be difficult to assess given that 68% may have extra-cranial disease and many (37–51%) have poor performance status, with Karnofsky performance status (KPS) <70 [3].

There are several validated scoring systems for prognosis following central nervous system (CNS) metastases including the Recursive

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Partitioning Analysis (RPA), Score Index for Radiosurgery (SIR), Basic Score for Brain Metastasis (BSBM), and the Graded Prognostic Assessment (GPA) [7,8]. The RPA is considered the gold standard for prognostic evaluation of patients with brain metastasis; however, the GPA recently outperformed the RPA in breast and small cell lung cancer populations [9,10]. The GPA has also performed well in patients with tumors rarely metastasizing to the CNS and is a more specific predictor of prognosis [11]. Neither index has been evaluated in the gynecologic population with brain metastasis.

Several treatment modalities are available for patients with brain metastasis including whole brain radiation therapy (WBRT), surgery or stereotactic radiosurgery (SRS) in combination with WBRT, and SRS alone [6,12–14]. Treatment selection is based on specific patient factors and prognosis, specifically, among patients for whom survival beyond CNS metastasis could extend >6 months. In this population, avoidance of WBRT or incorporation of hippocampal sparing techniques to avoid neuro-cognitive sequelae is indicated [6,13,14].

Our investigation characterizes presenting symptoms of CNS metastasis and evaluates RPA and GPA performance in predicting survival time and long term survivors (LTS) in the gynecologic oncology population. We assessed each treatment modality and its impact on CNS tumor control and rates of recurrence. Finally, we provide a detailed discussion of the role of radiation therapy and neurosurgical intervention in the treatment of CNS metastasis in the gynecologic oncology population.

Methods

After obtaining institutional review board (IRB #3746) approval, consecutive patients with brain metastasis from our institution were identified from radiation oncology and neurosurgery patient databases from 2005–2014 and selected if they had a primary diagnosis of ovarian, endometrial, or cervical cancer. Data were collected retrospectively from electronic medical records and abstracted for original diagnosis, stage at initial diagnosis, histology, symptoms at presentation of metastatic disease, number of metastasis, presence of extra-cranial disease, control of primary tumor based upon follow-up imaging, treatment modality, performance status, and survival. Survival was calculated from the date of diagnosis of brain metastases to date of death or last follow-up.

The decision to administer radiation therapy and the type of radiation therapy utilized was individualized at the level of the treating physician. The most commonly utilized regimens were WBRT 3000cGy given in 10 fractions or 3750cGy given in 15 fractions. If targeted stereotactic treatments were utilized, it was done in a single fraction (stereotactic radiosurgery) on a gamma knife (Elekta, Kungstensgatan, Stockholm) unit or in 3–5 fractions (stereotactic radiation therapy, SRT) on a linear accelerator. SRT doses varied from lesion to lesion depending on the size and location of the metastases and whether or not the patient had received prior radiation therapy to this region. The most commonly used SRT doses were either 25Gy in 5 fractions or 21Gy in 3 fractions.

Descriptive statistics were calculated. Patients were considered LTS if they survived 9 months or longer. The RPA (class I, II, or III) and GPA (0–1, 1.5–2.5, 3, 3.5–4) scores were calculated and grouped for each patient according to historical prognostic survival distributions from the literature (Table 1) [8]. To evaluate the predictive power of the RPA and GPA in the gynecologic population Kaplan–Meier curves were created and log-rank tests were performed to compare survival times. The proportion of long-term survivors by RPA and GPA group were compared using Fisher's exact test. Other individual prognostic factors were also evaluated using Kaplan–Meier curves and log-rank tests. Recurrence and treatment type were compared with Fisher's exact test. SAS version 9.3 (SAS Institute; Cary, NC) was used for statistical analyses.

Table 1
RPA and GPA scoring with LTS distribution.

	Died < 9 months	Lived ≥ 9 months	Censored before 9 months
RPA class			
Class I: Age < 65 years, KPS ≥ 70, controlled primary tumor, no extracranial metastases	1	1	1
Class II: All patients not in class I or III	13	8	1
Class III: KPS <70	10	0	0
GPA class[a]			
1: 0–1	13	3	0
2: 1.5–2.5	8	5	2
3: 3	3	0	0
4: 3.5–4	0	1	0

[a] Scoring: Age in years: 50–59 = 0.5, <50:1; KPS: 70–80 = 0.5, 90–100 = 1; number of CNS metastases: 2–3 = 0.5, 1 = 1; extracranial metastases: absent = 1.

Results

A total of thirty-five patients who had a primary diagnosis of a gynecologic malignancy and who either presented with or ultimately developed brain metastases were identified. Patient, tumor and treatment characteristics are shown in Table 2. Median age was 62 years (range, 41–78). The majority had ovarian cancer (54%); 37% had endometrial

Table 2
Patient demographics, presenting symptoms, and prognostic score.

	Overall sample (n = 35)	Ovary cancer (n = 19)	Endometrial cancer (n = 13)
Variable	*Median*	*Median*	*Median*
Age at original diagnosis (years)	59.3	50.9	62.0
Age at CNSmet diagnosis (years)	62.1	62.1	62.5
Time original treatment to CNSmets (years)	2.6	3.4	0.7
Cancer type	*n (%)*	*n (%)*	*n (%)*
Ovary	19 (54)	19 (100)	0
Endometrial	13 (37)	0	13 (100)
Cervix	3 (9)	0	0
Number of metastases			
1–2	14 (40)	5 (26)	6 (46)
3–8	10 (29)	7 (37)	3 (23)
Diffuse	11 (31)	7 (37)	4 (31)
KPS category			
≥70	25 (71)	13 (68)	9 (69)
<70	10 (29)	6 (32)	4 (31)
Treatment type			
WBRT	20 (57)	12 (63)	7 (54)
SRS	5 (14)	3 (16)	2 (15)
SBRT	2 (6)	0 (0)	2 (15)
Surgery	5 (14)	2 (11)	1 (8)
Hospice	2 (6)	1 (5)	1 (8)
Chemotherapy	1 (3)	1 (5)	0 (0)
Extracranial disease	32 (91)	17 (89)	12 (92)
Controlled primary	6 (14)	3 (16)	2 (15)
Symptoms (may have more than one symptom)			
Headache	20 (57)	12 (63)	7 (54)
Ataxia	6 (17)	2 (11)	2 (15)
Altered mental state	8 (23)	5 (26)	2 (15)
Dizzy	4 (11)	4 (21)	2 (15)
Seizures	4 (11)	2 (11)	1 (8)
N/V	3 (9)	2 (11)	1 (8)
Weakness	5 (14)	1 (5)	4 (31)
Stroke	5 (14)	2 (11)	2 (15)
Vision changes	1 (3)	0 (0)	1 (8)
GPA			
4 (best)	1 (3)	1 (5)	0 (0)
3 (middle)	3 (9)	1 (5)	1 (8)
2 (middle)	15 (43)	8 (42)	5 (38)
1 (worst)	16 (46)	9 (47)	7 (54)
RPA			
1 (best)	3 (9)	2 (11)	1 (8)
2 (middle)	22 (63)	11 (58)	8 (62)
3 (worst)	10 (29)	6 (32)	4 (31)