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Case series

Linear accelerator-based radiosurgery and hypofractionated stereotactic radiotherapy for brain metastasis secondary to gynecologic malignancies: A single institution series examining outcomes of a rare entity

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ABSTRACT

Objective: The use of SRS and fSRT to determine overall survival, tumor control, and local-disease free progression in patient diagnosed with gynecologic brain metastasis.

Methods: In this retrospective review, 11 patients aged 50 to 85 (median age of 71) were treated with linear accelerator-based SRS and hypofractionated SRT for brain metastasis secondary to gynecologic malignancies. In total, 16 tumors were treated from 2007 to 2017. Patients were treated to a median dose of 24 Gy (range 15 to 30 Gy) in 3 Fx (range 1 to 5). Median follow-up from SRS or SRT was 4 months (range 3–38 months).

Results: The actuarial 1-year overall survival rate was 26% with a median overall survival of 8 months. In addition, 1-year actuarial local control rate was 83.3% and the 1-year distant brain control rate was 31%. One patient experienced toxicity that presented as seizures after 7 months (due to minimal edema) that required anticonvulsants. There was no other acute or late treatment-related toxicity.

Conclusion: Linear-accelerator based SRS or fSRT is safe and effective for control of local tumor growth in brain metastases secondary to gynecologic malignancies. The course of disease remains aggressive as seen by poor overall survival and distant failure rate.

1. Background

In 2017, over 100,000 female gynecologic malignancies were diagnosed with a resultant 31,600 deaths (Andrews et al., 2004). Despite being common, gynecologic malignancies account for < 1% of brain metastasis (BM) < 3% of central nervous system (CNS) metastasis (Anupol et al., 2002). Specifically, the incidence of BM from ovarian, endometrial, and cervical cancer has been reported to be 0.3–2.2%, 0.4–1.2%, and 0.3–0.9%, respectively (Aoyama et al., 2006). This is mainly due to the "neurophobic" nature of gynecologic malignancies, meaning that they are rare manifestations of disease and typically arise as part of widespread and disseminated disease (Chang et al., 2009; Chen et al., 2010). Disseminated gynecologic metastasis is spread via hematogenous pathways, and historically has been postulated that the entire brain is seeded with micrometastatic disease, even if a single intracranial lesion is detected (Chen et al., 2010; Chura et al., 2007).

Without treatment, the prognosis of gynecologic malignancy to the brain is poor, with the median survival range rate around two months (Chang et al., 2009). The goal of treatment for BM is to eliminate the metastasis and to prevent recurrence in the brain (Kasper et al., 2017). Treatment of brain metastasis include surgical resection, irradiation, chemotherapy, and pharmacologic reduction of intracranial pressure. Given the difficulty of chemotherapeutic drugs to penetrate the blood-brain barrier, whole beam radiation therapy (WBRT) has served as the standard palliative therapy for BM, with a median survival rate of 2.5–4.5 months (Anupol et al., 2002; Keller et al., 2016; Kim et al., 2017). Also, administration of WBRT is associated with improvement of neurologic function in 50% of patients, with 70–80% citing an improved or stable neurologic state throughout their remaining life span (Ling et al., 2015).

In patients with truly limited intracranial disease, there is potential in replacement of WBRT by focal therapeutic options such as surgical resection or stereotactic radiosurgery (SRS), which can deliver high-dose and focal radiation (Chura et al., 2007). However, omission of WBRT has been shown to increase the risk of recurrent BM in patients, therefore surgical intervention (or SRS) with WBRT is frequently used

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to maximize disease control (Kim et al., 2017). Previous studies have shown that multimodal therapy that included surgery followed by adjuvant radiation and chemotherapy for solitary brain metastasis further increase median survival to 12–20 months, citing longer duration of neurologic improvement and lower rate of recurrence than patients treated with WBRT alone (Kasper et al., 2017; Keller et al., 2016; Ling et al., 2015).

Despite the reduction in brain recurrence and neurologic deaths, surgical intervention followed by WBRT (or WBRT alone) does not result in an increased actuarial survival or length of time patients were able to function independently (Kasper et al., 2017). However, because of the rarity of gynecologic BM, there are relatively few studies that evaluate the influence of stereotactic radiosurgery and radiotherapy on overall survival time, disease-free progression, and local control of gynecologic brain metastasis (Anupol et al., 2002; Aoyama et al., 2006; Kim et al., 2017; Matsunaga et al., 2016; McMeekin et al., 2001; Mehta et al., 2005). This study aims to evaluate the pre-existing literature and conduct an institutional analysis of patients treated with SRS and hypofractionated stereotactic radiotherapy (SRT) to determine survival, tumor control, and disease-free progression in patients diagnosed with gynecologic brain metastasis.

2. Methods

2.1. Patient population

This is a retrospective, institutional review board approved study from 2007 to 2017, in which 11 patients aged 50 to 85 (median age of 71) were treated with linear accelerator-based SRS and hypofractionated SRT for brain metastasis secondary to gynecologic malignancies. Two patients had primary diagnosis of cervical cancer, 3 had endometrial cancer, and 6 had ovarian cancer. In total, 16 tumors were treated. Furthermore, each patient had between 1 and 3 metastases, a median Eastern Cooperative Oncology Group (ECOG) performance status of 1 (range 0–3), and a median graded prognosis assessment (GPA) score of 2.5 (range 1–3). Five patients underwent previous surgical resection and the median time between primary diagnosis and development of brain metastasis was 28 months (range 0–139).

2.2. Treatment planning

All patients were immobilized with a Brainlab (Feldkirchen, Germany) relocatable mask system during stimulation and treatment. A gadolinium, contrast-enhanced T1-weighted neuronavigator Magnetic Resonance Image (MRI) was acquired with a resolution of 0.5 mm by 0.5 mm and a slice thickness of 2 mm. The patient was then fitted in with an immobilization system in the CT stimulation room. A mouth bite attached to the ring was placed against the upper dentition to prevent head tilt movement while the customized thermoplastic mask was molded. In some cases, the mouth bite was not used due to intolerance per the patient. A CT was acquired with a resolution of 1 mm by 1 mm and a slice thickness of 2 mm and was then rigidly registered to the MRI dataset in the Brainlab iPlan image software. The physician then contorted the gross target volume (GTV), which was expanded with 2 to 5 mm margin to generate the planning target volume (PTV). A treatment plan with 4 to 10 non-coplanar conformal arcs was generated using pencil beam algorithm in Brainlab iPlan Dose software. Patients were treated to a median dose of 24 Gy (range 15 to 30 Gy) in 3 Fx (range 1 to 5) prescribed to the 95–100% isodose line. Median SRS and SRT tumor volume was 3.025 cm^3 (range 0.21–68.5 cm^3) with a median total volume delivered of 8.88 cm^3 (range 1.28–68.5 cm^3). Alignment was confirmed with megavoltage cone beam prior to each treatment.

2.3. Statistical analysis

We reviewed each patients' record to determine local control, freedom from progression (local and distant), survival, and disease-free survival in patients. Statistical analysis was carried out using IBM® SPSS statistical software V20 and survival function curves (95% confidence interval) were created. Kaplan-Meier curves were used to illustrate overall survival (OS) and Cox and log-rank tests for statistical significance were used when appropriate.

Table 1
Characteristics of the 11 patients undergoing SRT/SRS for brain metastases secondary to gynecologic malignancies (2007–2017).

	Median (range)
Median age (in years)	71 (50–85)
Number of metastases	1 (1–3)
Eastern cooperative oncology group (ECOG) performance status	1 (0–3)
Graded prognostic assessment (GPA) Score	2.5 (1–3)
Prior WBRT	1 (9%)
Prior resection	5 (45%)
Treatment dose (in Gy)	24 (15–30)
Number of fractions (Fx)	3 (1–5)
Tumor volume (cc)	3.03 (0.21–68.5)
Planning target volume (cc)	8.88 (1.28–68.5)
Coverage (isodose line; in percentage)	95 (95–100)
Follow-up Time (in months)	58 (2–147)
Median number of follow-up MRIs	3 (1–9)

3. Results

From 2007 to 2017, 11 patients with a median age of 71 with a total of 16 metastatic tumors were treated with SRS or fSRT. Prior to radiotherapy, 1 patient had WBRT and 5 patients had previously undergone resection of brain metastasis. Median ECOG was 1 with a GPA of 2.5. Median follow-up was 58 months (range 2–147 months) after primary diagnosis and median follow-up from SRS or SRT was 4 months (range 3–38 months). Sixty-four percent of patients had follow up MRI available for review, with a median of 3 MRIs throughout that period (Table 1). Follow up MRIs were standard diagnostic MRIs with and without contrast (if possible).

Local recurrence was noted on MRI scans in two patients. These patients had re-irradiation, with one undergoing salvage conventional radiotherapy (XRT) in the posterior fossa after focal progression and the other undergoing WBRT for leptomeningeal failure. The 1-year actuarial local control rate was 83.3% (Fig. 1a). There were 3 patients who experienced distant brain failures; these occurred at 4, 8, and 9 months. This resulted in a 1-year distant control rate of 31%. (Fig. 1b). There was no difference in local control or overall survival based on primary malignancy, although our sample size was small. There was also no difference in rate of distant failure based on primary histology. After radiotherapy, 1 patient experienced toxicity that presented as seizures after 7 months due to minimal edema requiring levetiracetam and steroids. However, after review by neurosurgery it was decided that this patient did not require further surgery. There was no other acute or late ≥ grade 3 treatment-related toxicity.

The actuarial 1-year overall survival rate was 26% with a median overall survival of 8 months (Fig. 1c).

4. Discussion

Similar to systemic metastasis from lung, liver, and bone malignancies, brain metastasis from gynecologic cancers are considered a negative prognostic sign, with most patients developing these as a final stage of the progression from the primary cancer with worse systemic condition compared to other malignancies (Mehta et al., 2005). The advent of more potent chemotherapy regimens for gynecologic malignancies, as well as the increasing sensitivity of diagnostic techniques has allowed for the increased detection of unusual manifestations of