



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 cm³ (range 0.21–68.5 cm³) with a median total volume delivered of 8.88 cm³ (range 1.28–68.5 cm³). Alignment was confirmed with megavoltage cone beam prior to each treatment.

2.3. Statistical analysis

We reviewed each patients' record to determine local control,

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)

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.

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 \geq 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

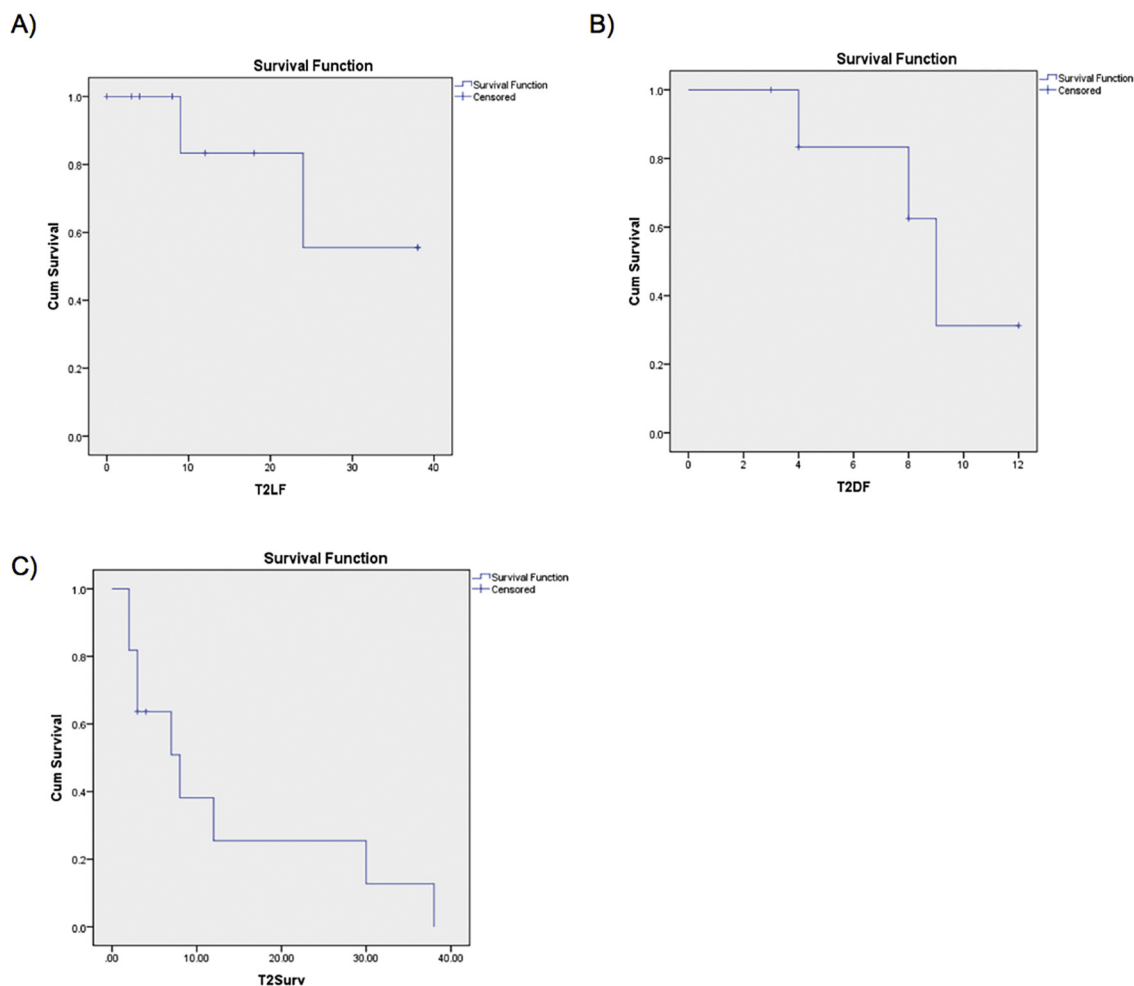


Fig. 1. Kaplan-Meier actuarial estimates for (A) local control (median could not be determined), (B) distant brain progression-free survival (median = 9 mo), and (C) overall survival (median = 8 mo).

treatment failure as the brain may be considered a “sanctuary site” for disease during systemic chemotherapy (Monaco et al., 2008; Niu et al., 2013). Regardless of therapy, brain metastases tend to have a median survival of three to six months (Patchell et al., 1998) compared to a median survival of only one month without treatment in the setting of gynecologic brain metastases (Ling et al., 2015).

The main role in the treatment of brain metastasis is to control or prevent any neurologic symptoms and to improve quality of life (Pectasides, 2006). As such, depending on patient presentation and disease status treatment options may range from surgery, WBRT, SRS, or some combination of the above. For patients with solitary lesions, large symptomatic lesions, or in a case where tissue is needed to confirm diagnosis, craniotomy is typically recommended. Based on the landmark trial by Patchell et al. (Kasper et al., 2017) radiation is typically delivered afterwards (either WBRT or SRS), to help prevent recurrence and decrease risk of neurologic death. That particular trial employed WBRT as adjuvant therapy, but in recent years for patients with limited lesions most centers now offer SRS to the resection bed to help avoid potential complications of WBRT (Piura & Piura, 2012; Rodriguez et al., 1992).

As implied above, WBRT is becoming increasingly omitted from the initial management strategy to reduce the risk of late radiation effects,

specifically neurocognitive deficits (Chura et al., 2007). Stereotactic radiosurgery and hypofractionated SRT offer an alternative approach to WBRT for brain metastases, allowing for delivery of a highly focused dose of radiation with rapid falloff to spare surrounding normal brain and organs at risk. In the early years of SRS, it was typically added as a boost to WBRT, as seen in RTOG 9508 where overall survival benefit was seen with SRS for patients with a single metastasis (Rwigema et al., 2011). Gradually, WBRT was omitted in the setting of limited metastatic intracranial disease, and was even condoned by ASTRO in their evidence-based review of the role of SRS for brain metastases, as to date omission or addition of WBRT does not appear to affect overall survival (Siegel et al., 2017). On the other hand, there is reasonably good evidence that those patients in which WBRT is omitted are at increased risk for distant brain failure. Results of a randomized Japanese trial comparing WBRT+SRS to SRS alone showed that the 12-month actuarial brain tumor recurrence in the SRS-alone group was 76.4% compared to 46.8% for the WBRT + SRS group ($p < 0.001$) (Chura et al., 2007). This difference highlights the need for vigilant follow up with MRIs, so that appropriate salvage therapy can be implemented when necessary.

Reviewing the current literature, (Anupol et al., 2002; Aoyama et al., 2006; Kim et al., 2017; Matsunaga et al., 2016; McMeekin et al., 2001;

Table 2

Summary of major series presenting outcomes of SRS as a treatment option for brain metastases secondary to gynecologic malignancies.

Series	Year	Patients (n)	Median Dose/ Fraction	Median progression-free survival (months)	Median overall survival (months)	12-month overall survival rate	12-Month distant brain progression-free survival rate	12-month local control rate
(Keller et al., 2016)	2016	33	20/1	7	15	54.9%	65.8%	84.3%
(Kim et al., 2017)	2017	11	19.3/1	12	17	90.1%	ND	ND
(Chang et al., 2009)	2009	30	19/1	10	15.2	63%	45%	67%
(Monaco et al., 2008)	2008	27	ND	ND	5	15%	ND	ND
(Kasper et al., 2017)	2016	8	16–22/1	ND	29 ^a	75%	50%	100%
(Matsunaga et al., 2016)	2016	70	20/1	ND	8	43.8%	ND	89.9%
Current series	2018	11	24/3	8	8	25.5%	31.3%	83.3%

^a OS reported from primary diagnosis in this study.

Mehta et al., 2005) there are a handful of series on SRS for brain metastases from gynecologic malignancies (Table 2). One of the original series by Monaco et al. (Matsunaga et al., 2016) included 27 patients, of which 66% had prior WBRT. All patients were treated in single fractions using Gamma Knife (dose not reported) and 66% of patients had follow up imaging. Local control was reported as 100% with no excess toxicity. Median overall survival was poor at 5 months. A more recent study by Kasper et al. (McMeekin et al., 2001) examined outcomes in 20 lesions treated in 8 patients, all with gynecologic primary malignancies. All patients were treated with robotic assisted LINAC-based SRS (Cyberknife™). The majority of lesions were treated in a single fraction to doses ranging from 16 to 22 Gy. One-year local control was excellent at 91%. Median overall survival was reported from primary diagnosis (not SRS), and was 29 months. No treatment related toxicities were observed.

Results of our study mirror those discussed above and presented in Table 2, showing excellent local control in the 80–90% range with low rates of toxicity. This study appears to represent the largest group of patients with brain metastases from gynecologic malignancies treated with a hypofractionated SRT approach, yielding similar results to traditional single fraction SRS. As is typical with small series such as this, caution must be used when interpreting results due to selection bias and sample size. Looking at the results in Table 2, one can see that overall survival seems to have improved over time in this patient population, likely due to advances in systemic therapy. As systemic therapy improves and patients live longer, the importance of intracranial control increases, with the goal of preventing neurologic-related death. Keeping that in mind, as patients live longer, without whole brain radiation, risk of distant relapse can be high, as distant failure was seen in almost 70% of patients in this study. This highlights the importance of surveillance MRIs and compliant patients that understand potential for development of new lesions.

5. Limitations

The standard limitations of a retrospective study involving a relatively rare condition (brain metastases from gynecologic malignancy) including selection bias and small sample size apply here. As indicated, brain metastasis from gynecologic malignancies is a rare event that typically occurs late in systemic disease with short survival, which can potentially skew local control results as well.

6. Conclusion

SRS and hypofractionated SRT remain a safe, reasonable, effective treatment option for brain metastases from gynecologic malignancies—which still remains a rather rare entity. As systemic therapy continues to evolve, and survival lengthens, intracranial control will continue to play a very important role.

Disclosures

The authors of this paper would like to declare that they have no financial or other conflicts of interest in relation to this research and publication.

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