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Original research article

Radiosurgery for brain metastases from ovarian cancer: an analysis of 25 years' experience with Gamma Knife treatment

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ARTICLE INFO

Article history:

Received 13 April 2019

Received in revised form

18 July 2019

Accepted 7 October 2019

Available online 30 October 2019

Keywords:

Gamma Knife

Radiosurgery

Brain metastases

Ovarian cancer

ABSTRACT

Purpose: We present our results in the treatment of brain metastases (BM) from ovarian cancer using Gamma Knife Radiosurgery (GKRS) over the last 25 years in a single institution. **Background:** Gamma Knife Radiosurgery has become increasingly important in the management of brain metastases from ovarian cancer due to improving results from systemic disease and the need for better outcomes.

Material and methods: The medical records of 9 patients with brain metastases from ovarian cancer treated with GKRS between 1993 and 2018 were reviewed. Median age at first treatment was 57 years (range 39–76). Forty-two brain metastases were treated with 16 procedures. Median tumor volume was 1.8cc ranging from 0.2 to 30.3cc (there were five patients with a tumor volume exceeding 10cc). Median prescription dose was 16 Gy.

Results: Using Kaplan Meier estimates, the median OS after diagnosis was 48.1 months and the median OS after GKRS was 10.6 months (ranging from 2.5 to 81 months). The Kaplan Meier survival rates were 31.3%, and 6.5% at 2 and 5 years after GKRS, respectively. Treatment procedure was well tolerated and no patient presented with acute or chronic toxicity. Two of 9 patients had a tumor requiring retreatment (local control of 95% 40/42). Two out of the 7 patients evaluated for cause of death expired due to progression of brain metastases and the remaining ones died of systemic disease with brain control.

Conclusions: GKRS for BM from ovarian cancer is a safe and effective modality. Our findings are in agreement with the recent literature indicating that women with brain metastases from ovarian cancer will benefit with radiosurgery and may achieve long term survival with brain control.

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1. Background

Cerebral metastases from gynecological tumors are rare and usually develop late in the course of the disease. The incidence of brain metastases in ovarian cancer is between 1 and

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<https://doi.org/10.1016/j.rpor.2019.10.004>

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3%, with a recent increase likely to be related to earlier diagnosis with modern imaging techniques (CT, MRI, PET) and more effective systemic therapies allowing prolongation of the patient's life.^{1,2} Dissemination is primarily via local spread in the peritoneal cavity, through the lymphatics mainly to retroperitoneal lymph nodes, and then via the hematogenous route most commonly to the liver and lungs and, eventually, to the brain via the pulmonary vasculature.^{3–5} The incidence of brain metastases in women with gynecological malignancies is low. They account for 1–2% of all brain metastasis, it's a vast majority of which originate from the lung, breast, and melanoma primaries.^{4,5} Metastatic brain lesions occur in 0.3–0.9% of uterine cancers, 1–3% of ovarian cancers, and 0.4–2.3% of cervical cancers.⁶ Life expectancy in these patients is poor. Typically, the treatment of brain metastasis in patients with ovarian cancer has consisted of a multimodal approach including surgery, radiation, and chemotherapy.⁷ Whole brain radiation therapy (WBRT) for brain metastases has not changed its poor prognosis and very short survival. Stereotactic radiosurgery (SRS) is becoming a new paradigm in the management of these patients, in which high doses of collimated radiation are delivered by a linear accelerator or by a Gamma Knife.⁸ The brain metastases from ovarian cancer are deemed to be good candidates for SRS because of the common involvement of the cortico-medullary junction; however, there is limited data on patients treated with Gamma Knife SRS (GKRS) from gynecological cancers.⁹ The primary objective of this study was to evaluate our results with GKRS for brain metastases (BM) in patients with ovarian cancer treated in our center over the last 25 years as, in general, it is not commonly a part of the management of these brain tumors.

Aim

Gamma Knife Radiosurgery has become increasingly important in the management of brain metastases from ovarian cancer due to improving results from systemic disease and the need for better outcomes.

2. Material and methods

2.1. Population

A retrospective analysis of all patients with ovarian cancer treated with GKRS at our outpatient center from October 1993 to January 2019 was performed.

Inclusion criteria included tissue-confirmed diagnosis of epithelial ovarian cancer with evidence of brain metastases as diagnosed by computed tomography (CT) and magnetic resonance imaging (MRI). Karnofsky score (KPS), age at diagnosis, radiosurgery dose, and survival time were analyzed. All patients signed an informed consent before treatment and underwent a complete workup before GKRS.

Of the 872 women diagnosed and treated for brain metastases in the center, nine had primary ovarian cancer (1.03%). At presentation, six of the 9 patients had a Karnofsky score of 90%, one patient had a Karnofsky score of 80%, and two patients had no documented score. The median age at first treatment was 57 years (range 39–76 years). All patients had

undergone resection of the primary ovarian cancer and had previously received chemotherapy. Table 1 shows the patients' characteristics and number of the lesions treated.

2.2. Radiosurgery

GKRS is a technique of radiotherapy that delivers a single high-dose fraction of radiation to the target using Cobalt 60 as a radioactive source. All patients were treated with a Gamma Knife (Elekta®, Stockholm, Sweden) models U, C and Perfexion which use 201, 201 and 192 radioactive sources, respectively. All unblocked beams converge to a fixed intersection point creating a treatment delivery volume that can be adjusted depending on the size and volume of the tumor. By the end of treatment, each portion of each target will have spent time in alignment with this fixed intersection point. Alignment is stabilized using a stereotactic frame fixed to the patient's head resulting in unsurpassed accuracy and precision.

The application of the stereotactic frame was performed using local anesthesia, IV sedation and all patients were treated on an outpatient basis at our freestanding facility. A brain MRI study with IV contrast (Gadolinium) enhancement was obtained in a 1.5 T magnet unit immediately prior to the treatment. Depending on tumor location, the following organs at risk were contoured: brainstem, optic chiasm, optic nerves, lens and any other pertinent structure.

Forty-two metastatic tumors were treated, ranging from 1 to 11 lesions. The median number of metastases treated with GKRS was 2, with a mean tumor volume of 3.5 cm³ (range 0.2–30.3 cm³).

Management of the primary disease consisted of a combination of surgery and chemotherapy. Prior to GKRS, two patients had craniotomy and three patients were treated with radiotherapy (RT) before GKRS. All the tumors were located in the cerebral parenchyma. Location of the tumors were in 62% supratentorial and in 38% infratentorial.

The forty-two brain metastases were treated with 16 procedures in the 9 patients. Median tumor volume was 1.8 cc ranging from 0.2 to 30.3cc (there were five patients with a tumor exceeding 10cc). Median prescription dose was 16 Gy (range 11–25 Gy).

2.3. Analysis

Patient characteristics, initial approach to ovarian cancer management, interval between primary diagnosis to brain metastases, treatment modalities, location and volume of brain metastases and survival outcomes were reviewed (Table 1).

The primary end-points of this study were: (1) overall survival (OS1) from the GKRS. (2) Overall survival time from the original diagnosis (OS2) as well as tolerance to the treatment were quantified. Kaplan–Meier analysis was used to calculate survival estimates of the study population Fig. 1.

3. Results

In this group of patients, the interval between diagnosis of ovarian carcinoma and development of brain metastases

Table 1 – Patient characteristics.

Characteristics	Median (range)	Mean	Total Number	Percentage
Interval between Primary Diagnosis and first GKRS treatment (months)	37.0 (8.0–126.7)		9	
Age at first GKRS treatment (years)	57 (39–76)	–	9	
KPS % at first GKRS treatment	90 (80–90)	–	7	
KPS 90%			6	86%
KPS 80%			1	14%
No. of brain metastases at first GKRS treatment	2 (1–11)	–		
1	–	–	4	44%
2	–	–	2	22%
4, 7, 11	–	–	3	33%
Location of brain metastases			42	
Supratentorial	–	–	26	62%
Infratentorial	–	–	16	38%
Tumor volume at GKRS (cm ³)	1.8 (0.2–30.3)	3.5		
Prescribed dose (Gy)	16.0 (11–25)	15.5		
Previous treatment				
Radiotherapy	–	–	3	33%
Chemotherapy	–	–	9	100%
Resection of primary	–	–	8	89%
Surgery of metastatic disease	–	–	2	22%

KPS: Karnofsky performance status; GKRS: Gamma Knife Radiosurgery.

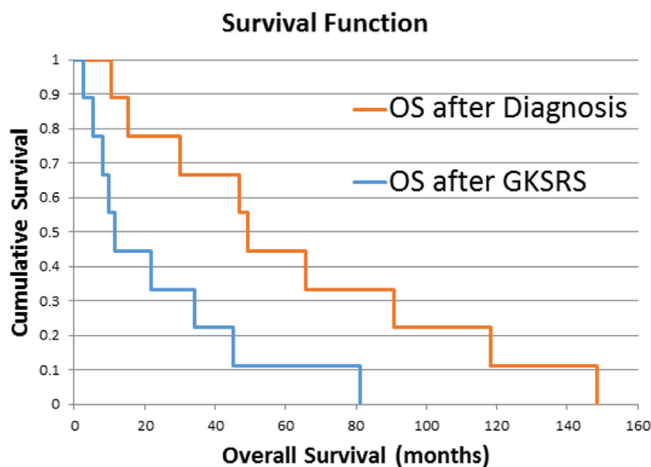


Fig. 1 – Kaplan-Meier curves of overall survival outcomes after first GKRS and after diagnosis: The median survival times were (10.6, 48) months. The survival rates were (31%, 71%) and (6.5%, 37%) at 2 and 5 years, respectively.

ranged from –1.0 to 125.5 months with a median of 31.5 months. The –1.0 stands for one patient whose brain metastasis was found a month prior to the primary tumor. The median overall survival time estimate from the original diagnosis of ovarian cancer (OS2) was 48 months, ranging from 10.6 to 148.4 months. The median overall survival after GKRS (OS1) was 10.6 months ranging from 2.5 to 81.1 months. The survival rates were 31.3%, and 6.5% at 2 and 5 years after GKRS, respectively (Table 1).

Two patients had a tumor requiring retreatment indicating local control of 95% (40/42) of tumors Fig. 2. Nine patients expired, two women expired due to progression of BM, and 5 died of systemic disease with brain control. One patient expired due to a ruptured intracranial aneurysm. The cause of death for the remaining two patients could not be determined.

None of the treated women developed treatment related toxicity.

4. Discussion

Epithelial ovarian cancer is the most lethal of the gynecology cancers with a 5-year survival rate of less than 50%. In the United States, it is estimated that about 22,000 women are diagnosed with the disease and 14,000 women die from the disease annually (7). Brain metastases from ovarian cancer are rare and uniform criteria for management of this diagnosis are not well established. In this review of 25 years of experience with 872 women diagnosed and treated for brain metastases in our center, nine (1.03%) had primary ovarian cancer with data in agreement with the literature. Traditional management of brain metastases from ovarian cancer has consisted of corticosteroids and whole brain radiotherapy. Surgery has not been a useful strategy due to a limited survival and, sometimes, a poor general status.

Whole brain radiation therapy (WBRT) alone has increased overall survival in previous cases, with a median survival of 2.5–4.5 months and, when combined with chemotherapy, survival has further increased to 10 months.¹⁰ In patients with multimodal therapy using surgery or SRS, survival after diagnosis may increase considerably. Lee et al. reviewed patients with brain metastasis from ovarian cancer treated with GKRS, and median survival was 29 months compared to 6 months of patients treated with WBRT.¹¹ Other treatment strategies are currently on development but multimodal therapy has increased the overall median survival to 20 months.¹² Piura et al. reviewed median survival times after diagnosis of ovarian carcinoma and found ranges from 24 to 67 months (median of 33 months), and the survival time after diagnosis of brain metastases ranged from 1 to 28 months (median of 6 months).⁶ Our results with a median overall survival after GKRS (OS1) of 10.6 months and median overall survival since the time

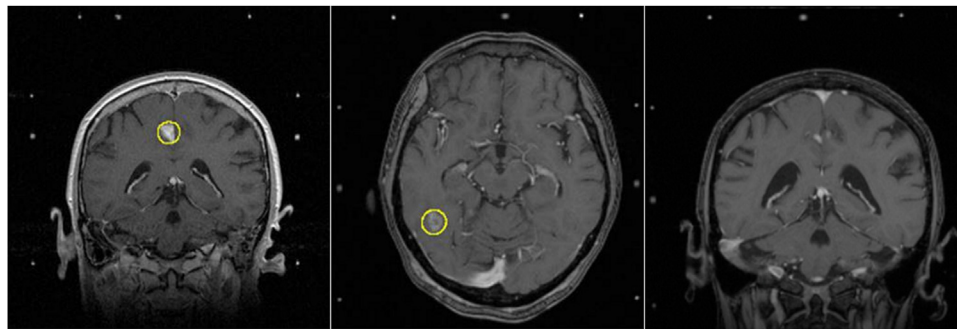


Fig. 2 – Planning MRI in coronal and axial planes (left and middle images) outlining two targets in a patient who survived for 81 months with a total of 3 lesions treated in two procedures; one in 1994 and another in 1997. The coronal image in the right demonstrates significant resolution of the disease upon follow-up.

of diagnosis of primary ovarian cancer (OS2) of 48 months compare well with the above reports. This suggests that GKRS is a good treatment option for controlling brain metastases from ovarian cancer in selected patients. Survival figures will likely improve when better systemic therapies become available since most patients fail due to extracranial progression of the disease.

Age, KPS score, number of metastases and histologic subtype are important elements that should be considered in the selection of optimal therapy for each patient.¹³ Our study did not analyze performance status; however, KPS greater than 70 has been shown by several studies to impact survival.^{8,14,15} Of the 7 patients with documented KPS, all had KPS >70.

GKRS seems to be associated with increased survival rates and acceptable toxicity as shown in our review and consistent with recently published results in the literature.^{16–18}

5. Conclusions

Treatment of brain metastases has evolved over the years and currently includes surgical resection, radiotherapy and/or chemotherapy. In general, the median survival after diagnosis of brain metastases is about 6 months; nevertheless, better survival can be achieved when multimodality therapy is used.

Results of radiosurgery for treatment of ovarian brain metastases are encouraging in terms of palliation of symptoms and improved prognosis as demonstrated in our review. Our small series demonstrates that GKRS is a valuable modality for management of brain metastases from ovarian cancer. It is minimally invasive and well tolerated. Although this study should be interpreted with caution because of the limited number of patients, our results are in accordance with the current published literature. GKRS should be considered as the first option for patients with BM from ovarian cancer independent of primary status.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Iftode C, D'Agostino GR, Tozzi A, et al. Stereotactic body radiation therapy in oligometastatic ovarian cancer: a promising therapeutic approach. *Int J Gynecol Cancer* 2018;28(8):1507–13.
2. Deng K, Yang C, Tan Q, et al. Sites of distant metastases and overall survival in ovarian cancer: a study of 1481 patients. *Gynecol Oncol* 2018;150(3):460–5.
3. Amendola MA, Walsh JW, Amendola BE, Tisnado J, Hall DJ, Goplerud DR. Computed tomography in the evaluation of carcinoma of the ovary. *J Comput Assist Tomogr* 1981;5(2):179–86.
4. Matsunaga S, Shuto T, Sato M. Gamma Knife Surgery for Metastatic Brain Tumors from Gynecologic Cancer. *World Neurosurg* 2016;89:455–63.
5. Piura E, Piura B. Brain metastases from ovarian carcinoma. *ISRN Oncology* 2011:527453.
6. Sadik ZHA, Beerepoot LV, Hanssens PEJ. Efficacy of gamma knife radiosurgery in brain metastases of primary gynecological tumors. *J Neurooncol* 2019, <http://dx.doi.org/10.1007/s11060019030942>.
7. Fields EC, McGuire WP, Lin L, Temkin SM. Radiation treatment in women with ovarian cancer: past, present, and future. *Front Oncol* 2017;7:177.
8. Lassman AB, DeAngelis LM. Brain metastases. *Neurol Clin* 2003;21:1–23.
9. Kim TJ, Song S, Kim CK, et al. Prognostic factors associated with brain metastases from epithelial ovarian carcinoma. *Int J Gynecol Cancer* 2007;17:1252–7.
10. Anupol N, Ghamande S, Odunsi K, Driscoll D, Lele S. Evaluation of prognostic factors and treatment modalities in ovarian cancer patients with brain metastases. *Gynecol Oncol* 2002;85:487–92.
11. Lee YK, Park NH, Kim JW, Song YS, Kang SB, Lee HP. Gamma-knife radiosurgery as an optimal treatment modality for brain metastases from epithelial ovarian cancer. *Gynecol Oncol* 2008;108(3):505–9.
12. Geisler LP, Geisler HE. Brain metastases in epithelial ovarian carcinoma. *Gynecol Oncol* 1995;57:246–9.

13. Pakneshan S, Safarpour D, Tavassoli F, Jabbari B. Brain metastasis from ovarian cancer: a systematic review. *J Neurooncol* 2014;**119**(Aug (1)):1–6.
14. Ogawa K, Yoshii Y, Aoki Y, et al. Treatment and prognosis of brain metastases from gynecological cancers. *Neurol Med Chir (Tokyo)* 2008;**48**:57–62.
15. Hong KS, Jeong HK, Do HL, et al. Clinical outcomes of gamma knife radiosurgery for metastatic brain tumors from gynecologic cancer: prognostic factors in local treatment failure and survival. *J Korean Neurosurg Soc* 2016;**59**(4):392–9.
16. De Felice F, Marchetti C, Di Mino A, et al. Recurrent ovarian cancer: the role of radiation therapy. *Int J Gynecol Cancer* 2017;**27**(May (4)):690–5.
17. Jiang G, Balboni T, Taylor A, Liu J, Lee LJ. Palliative radiation therapy for recurrent ovarian cancer: efficacy and predictors of clinical response. *Int J Gynecol Cancer* 2018;**28**(Jan (1)):43–50.
18. Nikolaoul M, Stamenković S, Stergiou C, Skarleas C, Torrens M. Management of brain metastasis in a patient with advanced epithelial ovarian carcinoma by gamma-knife radiosurgery. *Srp Arh Celok Lek* 2015;**143**(3–4):205–9.