Management of Brain Metastasis in a Patient with Advanced Epithelial Ovarian Carcinoma by Gamma-Knife Radiosurgery

Marinos Nikolaou[1], Srdjan Stamenković[2], Christos Stergiou[3], Christos Skarleas[3], Michael Torrens[3]

[1]Department of Obstetrics and Gynecology, General Hospital of Agios Nikolaos, Lasithi, Crete, Greece;
[2]Department of Obstetrics and Gynecology, University Women's Hospital in Neuenheimer Feld, Heidelberg, Germany;
[3]Ganmma Knife Department, Hygeia Hospital, Marousi, Athens, Greece

SUMMARY

Introduction Brain metastases from epithelial ovarian cancer (EOC) are rare events. We present a rare case of single ovarian cancer metastasis to the brain treated with gamma-knife radiosurgery (GKRS).

Case Outline A 65-year-old woman with advanced EOC presented with severe neurologic symptoms. A single brain metastasis of 3.2 cm with surrounding edema in the left parietal lobe was detected by brain magnetic resonance imaging (MRI) scan during the work-up. The decision to perform GKRS was due to a surgical inaccessibility of intracranial lesion. Twelve weeks after the procedure, the MRI scan showed reduction in the diameter of brain metastasis and surrounding edema and the patient returned to good mental and motor performance. The patient survived for 22 months following treatment and died from a progressive intra-abdominal disease. Prognosis of ovarian cancer patients with brain metastases is generally poor regardless of treatment.

Conclusion Our case shows that GKRS as primary treatment modality for the control of ovarian cancer metastases to the brain was effective and can be considered as a treatment of choice if international selection criteria are followed.

Keywords: gamma-knife stereotactic radiosurgery; solitary brain metastasis; ovarian carcinoma

INTRODUCTION

Epithelial ovarian cancer (EOC) is the leading cause of mortality among gynecologic malignancies in the developed countries [1]. In recent decades, the natural course of the disease has changed as a result of better primary control of intra-abdominal disease with platinum-based chemotherapy. The patients with ovarian carcinoma have longer survival and develop recurrences in rare sites after initial treatment [2].

Brain is an unusual site for metastases from a primary EOC, with an estimated range of incidence of 1-3% [3]. In an autopsy study, Mayer et al. [4] reported an incidence of 0.87% in 576 autopsies of patients with EOC. However, some recent reports suggest an increased incidence of ovarian cancer metastases to the brain in patients with prolonged survival as a late manifestation of disease [5]. Most of the patients with ovarian cancer metastases to the brain have advanced stage disease at the time of diagnosis and poor long-term prognosis regardless of treatment [6, 7].

Due to the rarity of this entity, published guidelines are based on evidence from case reports and small clinical series [3]. Therefore issues concerning management and follow-up of these patients require specific consideration due to limited data that exist in the literature. During the last years, more aggressive treatments for ovarian cancer metastases to the brain have been promoted, including surgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) and chemotherapy alone or in combination [8]. This therapeutic approach may produce prolongation of patient survival and in some cases long-term remissions.

Gamma-knife radiosurgery (GKRS) is an alternative treatment option in selected cases without symptoms of brain compression [9]. It is particularly useful in surgically inaccessible lesions or where surgical resection is contraindicated due to co-morbidities. However, very few studies in the literature have investigated the role of GKRS in the management of ovarian cancer metastases to the brain [10-17].

We report a rare case of a patient with advanced stage EOC treated with GKRS for solitary ovarian cancer metastasis to the brain. The aim of this report is to record the therapeutic impact of GKRS on the patient's quality of life and survival.

CASE REPORT

A 65-year-old woman with advanced EOC disease (stage IIIc according to the International Federation of Gynecology and Obstetrics-FIGO) presented to our institution with severe neurologic symptoms. Eight years earlier, she

Correspondence to:
Marinos NIKOLAOU
Dept. of Obstetrics and Gynecology
General Hospital of Agios Nikolaos
Lasithi, Crete 72100
Greece
nikolaoumarinos@yahoo.gr

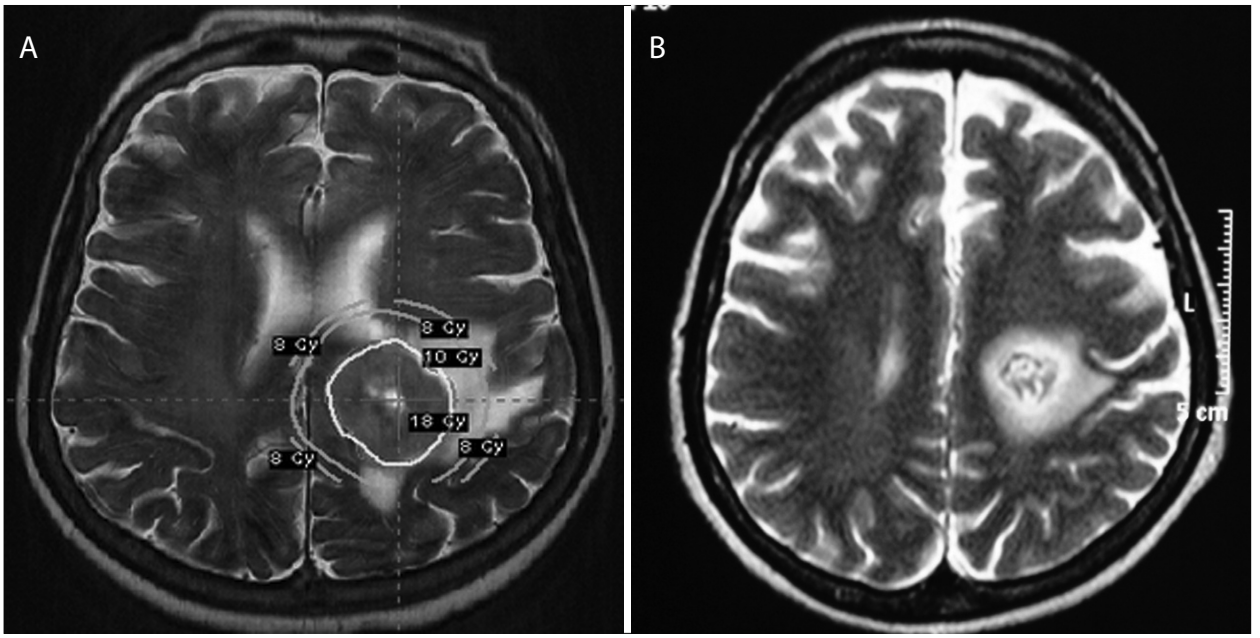

Figure 1. Axial T2-weighted brain MRI scan shows a solitary metastatic lesion in the left parietal lobe at the time of GKRS, with the treatment isodoses superimposed (A), and three months later with significant shrinkage of the tumor and reduction of edema (B)

had been treated with optimal cytoreductive surgery after detection of an endometrioid adenocarcinoma of low differentiation in the left ovary. A 6-course multi-agent chemotherapy was followed, with paclitaxel 280 mg and carboplatin 600 mg every 21 days with good response. Afterwards, hormonal therapy started, due to elevated levels of the tumor marker CA-125 (>90 IU/ml), with oral tamoxifen once a day.

Three years later a hard mass was found in her inguinal area and the lymph nodes surgically removed were positive for metastasis. New 6-course chemotherapy with paclitaxel 280 mg and carboplatin 600 mg every 21 days was started. At the end of this treatment, the patient had a complete resolution of the disease and was followed up regularly. Two years later, a left para-aortic lymphatic block was found by the abdominal computerized tomography (CT) scan, which proved to be metastatic on positron emission tomography (PET) scan and 6-course chemotherapy with cisplatin 130 mg and docetaxel 129 mg every 3 weeks was followed. Six months later, due to an increase in the diameter of the lymphatic block, a new course of chemotherapy with liposomal doxorubicin 600 mg (1st and 29th day) and gemcitabine 1500 mg IV (1st and 8th day) was given.

In February 2009, at the end of the above therapy, she started to have difficulty in walking and limitation in the movement of the right leg. The brain CT and MRI-examination revealed a 3.2-cm mass with surrounding edema in the left parietal region (Figures1A and 2A).

Immediately, high-doses of intravenous corticosteroids (dexamethasone 32 mg daily) and prophylactic anticonvulsant medications were used for the palliation of mass effect and seizures, respectively. Surgical resection was relatively contraindicated due to the position of the lesion in the dominant hemisphere, and therefore it was decided to perform GKRS with a Leksell Gamma Knife (Electra AB®, Stockholm, Sweden). Before the procedure stereotactic MRI was performed using a double dose of Gadolinium contrast agent and T1 slices (1.5 mm) were used for target coordinate determination and image directed dose planning.

The target was outlined without margins using Leksell GammaPlan and treated with a prescription dose of 18 Gy in one fraction prescribed to the 50% isodose with 93% coverage. The target volume was 18.8 cc, maximum dose 36 Gy, mean dose 23.5 Gy, Paddick conformity index 0.84 and gradient index 3.2. The procedure was well tolerated by the patient and there were no complications.

Three months after the procedure, the MRI showed reduction in the diameter of ovarian cancer metastasis to the brain (2.0 cm) and surrounding edema and the patient returned to good mental and motor performance (Figures 1B and 2B).

Twelve months after GKRS, chemotherapy for coexistent intra-abdominal recurrence of the disease with paclitaxel was initiated once a week for 12 weeks. This was discontinued because of the disease progressive course and was followed with oral etoposide for 3 months. The patient was followed up and died 22 months after the initial manifestation of the brain metastasis without any sign of cerebral involvement or any other neurological symptoms due to disseminated intravascular coagulation from the ileus.

DISCUSSION

Ovarian cancer metastases to the brain are rarely observed in comparison to other primary tumors [3]. Clinical manifestations are highly variable depending on the location of brain metastases. Patients usually complain of various neurological symptoms such as headache, neurologic deficits, altered mental status, confusion and seizures [3]. In our case, right lower extremity motor weakness was the

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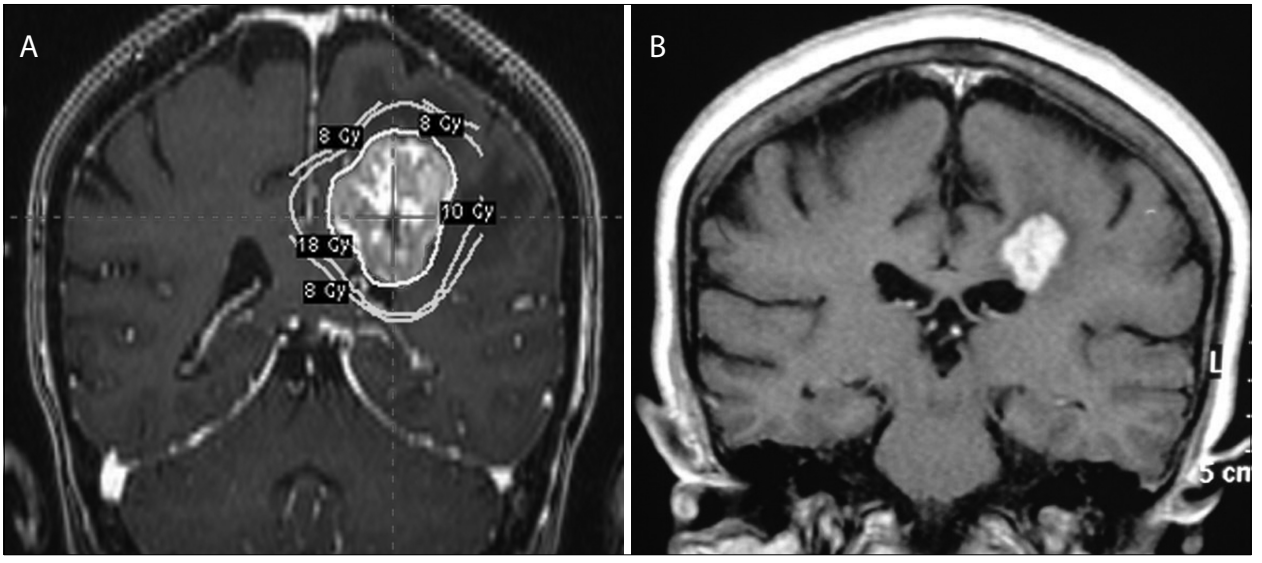

Figure 2. Coronal contrast-enhanced T1-weighted brain MRI scan shows the metastatic lesion at the time of treatment (A) and with decreased size at 3 months after GKRS (B)

main presenting sign, followed rapidly by altered mental status and confusion.

Routine brain imaging studies are not recommended in the follow-up procedures after primary treatment. So, a high level of clinical suspicion is required by clinicians in EOC patients presenting with neurological symptoms.

Management of ovarian cancer metastases to the brain has evolved over years from WBRT and corticosteroids to multimodal therapy achieving median survival of more than 20 months [3, 8, 11]. The treatment modality is dependent on several factors, including the number and location of metastases, the general status of the patient, the presence of active intra-abdominal disease and the history of previous treatments [7]. In our patient, surgical resection was contraindicated due to inaccessibility and we decided to perform GKRS.

Selection criteria for patients with ovarian cancer metastases to the brain who will benefit from GKRS help to guide treatment decisions and evaluate prognostic factors [15]. GKRS is especially useful for patients with single ovarian cancer metastases to the brain who are unable to tolerate surgery and for those with surgical inaccessible lesions [6]. However, a recent prospective observational study showed that GKRS might be a suitable alternative for patients with up to ten cancer metastases to the brain for initial treatment as it was not inferior to that for patients with two to four cancer metastases to the brain in terms of overall survival [18, 19]. So, selection criteria for patients with cancer metastases to the brain who will undergo GKRS are up to 10 brain metastases, maximum diameter of tumor <4 cm, minimal mass effect, inaccessible lesions and total tumor volume of <15 cm^3. On the contrary, the exclusion criteria are a poor medical condition and/or the presence of carcinomatous meningitis [16, 19].

However, limited data in the literature are available on the management of ovarian cancer metastases to the brain using GKRS. The first report by Kawana et al. [10] described a patient with multiple ovarian cancer metastases to the brain treated by a multimodality approach including GKRS which produced complete remission for 21 months with good quality of life. In the case of Anupol et al. [11], a patient treated with GKRS and chemotherapy for the second brain recurrence after 22 months of initial multimodal therapy had survival prolonged for another 27 months. Another case report by Shiohara et al. [12] recorded a survival of greater than 38 months from radiosurgery treatment but Monaco et al. [13] in a series of 27 patients (22 ovarian and 6 endometrial) found a much poorer mean survival of only 5 months despite effective control of all brain lesions. It is evident that survival is not the best index for the evaluation of radiosurgery since it depends mostly on extracranial disease status. Local brain control is a better index. Brown et al. [14] achieved local control of ovarian cancer metastases to the brain and prolongation of survival in three ovarian cancer patients with multimodality therapy including GKRS. In a small clinical series of 13 patients with ovarian cancer metastases to the brain, the multivariate analysis showed that including GKRS was the most important prognostic factor affecting the survival time [15]. Furthermore, seven patients with ovarian cancer metastases to the brain treated with GKRS achieved a longer median survival period than those treated with WBRT, 29 months versus 6 months, respectively [16]. In addition, a recent study by Navaro-Martin et al. [17] reported that GKRS provided excellent local control of solitary ovarian cancer metastasis to the brain and mean survival of 23.6 months in three EOC patients. In the present case, GKRS resulted in the local control of a solitary ovarian cancer metastasis to the brain, good quality of life and survival of 22 months.

GKRS has a number of advantages in the management of metastatic disease of the brain which have been enumerated by Linskey et al. [20] in a recent evidence-based clinical practice guideline. Combining radiosurgery (RS) with WBRT improves survival but RS is superior to WBRT for up to 3 metastases. RS+WBRT provide equal survival

to surgery+WBRT and indeed RS alone may be equivalent to surgery+WBRT. Since RS is quicker and easier for the patient and had fewer complications than surgery it would seem to be the method of choice in most cases. RS has been shown to be more cost-effective than surgery with approximately half the average cost per week of survival [21, 22]. RS is also less likely to cause cognitive defects than WBRT [23]. Accordingly, the method has been approved for routine funding by the National Health System in the UK provided certain criteria are met [24].

This combination of clinical and cost effectiveness, together with the high level of local control reported for GKRS in ovarian cancer metastases to the brain, as summarized in this paper, indicate that the method is likely to become the method of choice in cases where the intervention is indicated. The indication for treatment implies a reasonable prognosis for the systemic disease such as potential survival greater than 6 months that is usually judged based on prognostic criteria such as the Brussels score for brain metastases [25].

As overall survival has increased due to improvements in the management of primary disease, more EOC patients will present with ovarian cancer metastases to the brain in the future. Currently, there is relatively less experience with GKRS as the treatment modality because of the clinical rarity of ovarian cancer metastases to the brain but the initial results are encouraging in terms of palliation of symptoms and improved prognosis. Further studies with multicenter participation are needed to confirm its efficacy in the management of ovarian cancer metastases to the brain but, in the meantime the results from other diagnoses suggest that GKRS should be the method of choice in most cases.

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Лечење метастазе у мозгу код жене са узнапредовалим епителним карциномом јајника радиохируршки гама-ножем

Маринос Николау[1], Срђан Стаменковић[2], Христос Стерију[3], Христос Скарлеас[3], Мајкл Торенс[3]

[1]Одсек за гинекологију и акушерство, Општа болница „Свети Никола", Ласити, Крит, Грчка;
[2]Одсек за гинекологију и акушерство, Универзитетска болница за лечење жена у Нојенхајмер Фелду, Хајделберг, Немачка;
[3]Одсек за гама-нож, Болница Хигија, Маруси, Атина, Грчка

КРАТАК САДРЖАЈ

Увод Метастазе у мозгу код жена с епителним карциномом јајника су веома ретке. Представљамо редак случај болеснице с метастазом на мозгу пореклом од епителног карцинома јајника која је лечена радиохируршки гама-ножем (енгл. *gamma-knife radiosurgery – GKRS*).

Приказ болесника Приказана је жена стара 65 година са узнапредовалим епителним карциномом јајника и тешким неуролошким симптомима. На снимку магнетне резонанције (*MRI*) уочени су солитарна метастаза пречника 3,2 *cm* и едем околног можданог ткива, локализовани у паријеталном режњу. Одлука о примени *GKRS* била је условљена неприступачношћу интракранијалној лезији. Дванаест недеља касније применом *MRI* утврђено је значајно смањење метастазе у мозгу и околног едема, као и побољшање менталног стања и моторике болеснице. Болесница је преживела још 22 месеца, а смртни исход је наступио услед прогресије тумора у абдомену. Прогноза код жена с карциномом јајника и метастазама у мозгу је веома лоша без обзира на врсту лечења којем су подвргнуте.

Закључак У приказаном случају се види да је *GKRS*, као терапија избора код можданих метастаза у оквиру карцинома јајника, била успешна и може се прихватити као терапија избора код добро одабраних болесница поштујући међународне критеријуме.

Кључне речи: стереотаксична радиотерапија гама-ножем; солитарна мождана метастаза; карцином јајника

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