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Citation

Kasper, Ekkehard, Franziska Ippen, Eric Wong, Eric Uhlmann, Scott Floyd, and Anand Mahadevan. 2017. "Stereotactic radiosurgery for brain metastasis from gynecological malignancies." *Oncology Letters* 13 (3): 1525-1528. doi:10.3892/ol.2017.5621. <http://dx.doi.org/10.3892/ol.2017.5621>.

Published Version

doi:10.3892/ol.2017.5621

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Stereotactic radiosurgery for brain metastasis from gynecological malignancies

EKKEHARD KASPER¹, FRANZISKA IPPEN¹, ERIC WONG², ERIC UHLMANN²,
SCOTT FLOYD³ and ANAND MAHADEVAN³

Departments of ¹Neurosurgery, ²Neuro-oncology and ³Radiation Oncology, Beth Israel
Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

Received April 5, 2015; Accepted April 15, 2016

DOI: 10.3892/ol.2017.5621

Abstract. Brain metastases are relatively uncommon in gynecological malignancies, and there is limited available data on their management. The present study reports the outcomes of patients with brain metastasis from gynecological malignancies who were treated with stereotactic radiosurgery (SRS). Patients with brain metastasis from a gynecological primary site were treated with SRS using the Cyberknife™ frameless SRS system. Primary lesions were treated with a single fraction of 16-22 Gy. A total of 3 resection cavities were treated with 8 Gy 3 times, meaning a total of 24 Gy, and 1 recurrent lesion was re-irradiated with 5 Gy 5 times, meaning a total of 25 Gy. All patients were followed up with regular magnetic resonance imaging and clinical examinations 1 month after treatment and every 2 months thereafter. A total of 20 lesions in 8 patients were included in this study; 1 patient presented with metastatic endometrial cancer and the remaining 7 presented with metastatic ovarian cancer. The median age was 61 years (range, 48-78 years). All patients had received systemic therapy prior to developing brain metastasis. A total of 3 patients underwent surgical resection and 1 patient was administered re-irradiation for recurrence. There were 3 local failures in 2 patients. The actuarial 1-, 2- and 3-year local control rates were 91, 91 and 76%, respectively. The median overall survival time was 29 months. No SRS-associated toxicities or neurological mortalities were observed. In conclusion, brain metastasis from gynecological malignancies is uncommon, however, SRS is a safe and effective treatment modality for local control as a primary or adjuvant treatment in patients with this disease.

Introduction

Cervical cancer is the twelfth most common malignancy in women in the USA, with 12,340 cases annually. The cancer is the second leading cause of cancer-associated mortality in women aged 20-39 years, and 4,030 patients succumb to the disease every year (1). Cervical cancer is also the third most common cancer worldwide, with an annual incidence of 530,000 cases and 250,000 mortalities expected in 2011 (2,3). Endometrial carcinoma is the most common malignancy of the female genital tract in the United States, with an estimated incidence of 49,560 cases and 8,190 mortalities annually (1). Ovarian cancer is the fifth most common cancer in women, with an estimated 22,240 new cases annually, resulting in 14,030 mortalities, as it often presents with widespread metastasis (1). Ovarian cancer often spreads loco-regionally in the abdomen and distant metastasis are infrequently observed (4). Amongst these abdominal diseases, brain metastases from malignancies of the female genital tract have rarely been reported, with an incidence of only 0.4-1.2% in metastatic cervical cancer patients (5-7), 0.3-0.9% in the majority of metastatic endometrial cancer cases (4,8) and <2% in metastatic ovarian cancer cases (9,10). Despite decades of studies on the management of brain metastases from lung, renal and gastrointestinal cancer, melanoma and other cancers, there is hardly any available literature on brain metastases from gynecological malignancies. Furthermore, other than results from case series, there are few guidelines on how to manage these patients.

There have been significant advances in the systemic management of metastatic cervical, endometrial and ovarian cancer (11-13). This has been purported to increase recognition of unusual metastatic sites such as the brain (14-17). These advances have also led to prolonged survival in such patients, meaning that quality of life, including neurocognitive effects, is an important consideration. In consideration of these facts, the present study reports the cases of a series of patients with brain metastasis who were treated in Beth Israel Deaconess Medical Center (Harvard Medical School, Boston, MA, USA) with stereotactic radiosurgery (SRS).

Correspondence to: Dr Anand Mahadevan, Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA
E-mail: amahadev@bidmc.harvard.edu

Key words: stereotactic radiosurgery, gynecological malignancy, brain metastasis

Patients and methods

Patients. From a database of >1,045 patients with brain metastases who were treated with SRS in

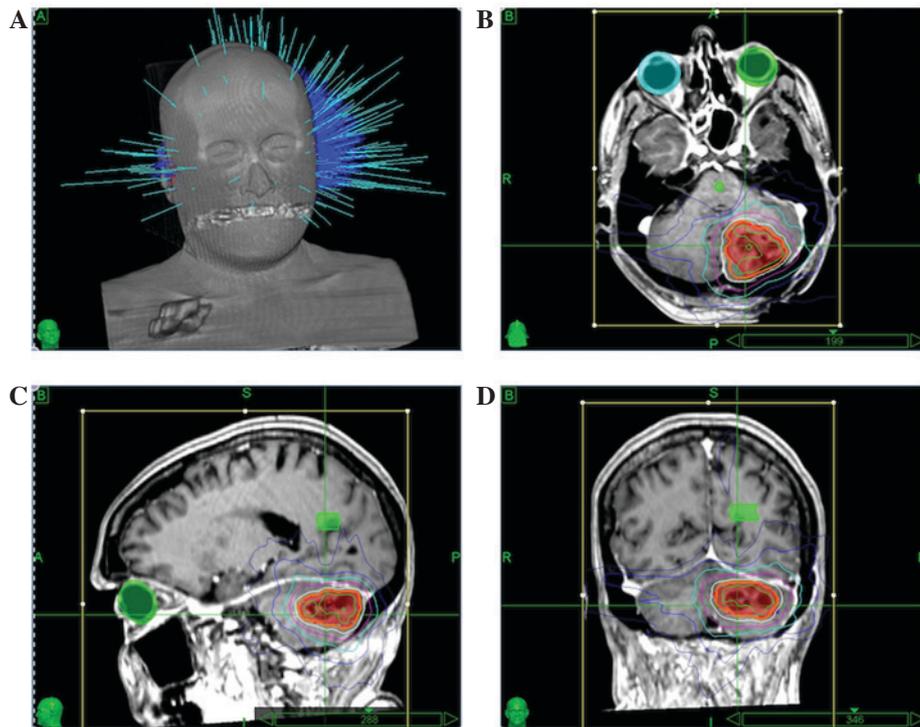


Figure 1. Representative stereotactic radiosurgery treatment of cerebellar metastasis showing (A) a non-isocentric beam profile, and (B) axial, (C) sagittal and (D) coronal magnetic resonance images, with dose distribution.

Beth Israel Deaconess Medical Center between January 2006 and February 2013, 8 patients with 20 lesions treated by SRS for brain metastasis from gynecological malignancies were identified. The medical records, including radiology and pathology records, were reviewed retrospectively for the study. The present study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Examination and treatment of patients. All patients were reviewed in the multidisciplinary brain tumor clinic and underwent diagnostic gadolinium-enhanced magnetic resonance imaging (MRI; GE Healthcare Bio-Sciences, Pittsburgh, PA, USA). The Cyberknife™ robotic SRS system (version 8.5, Accuray, Inc., Sunnyvale, CA, USA) was used to treat these patients. Prior to treatment, the patients were simulated with aquaplast (QFix, Avondale, PA, USA) mask immobilization and contrast enhanced computed tomography (CT; Toshiba American Medical Systems, Glen Mills, PA, USA) of 1-mm thickness were performed. CT MRI fusion was obtained using Multiplan™ (version 3.5; Accuray, Inc.) and the treating radiation oncologist and neurosurgeon delineated all target volumes. A representative treatment plan is shown in Fig. 1.

The enhancing tumor or resection cavity was identified as the target volume. A total 2-mm expansion for the planning target volume was awarded to resection cavities. Doses of 16, 18 or 22 Gy were prescribed to lesions measuring >3, 2-3 and <2 cm, respectively. Lesions >5 cm or resection cavities received fractions of 8 Gy 3 times, meaning a total of 24 Gy delivered on 3 consecutive days. Similarly, patients who had received prior SRS were re-irradiated with 5 Gy 5 times,

meaning a total of 25 Gy. The prescription isodose line that covered at least 95% of the target volume was chosen. All patients were pre-medicated with 4 mg dexamethasone twice a day, starting on the day of treatment, which was tapered off after treatment by 2 mg every 3 days, and patients with supratentorial lesions received seizure prophylaxis with levetiracetam at a dose of 1,000 mg twice a day for 1 week from the day of treatment.

Follow-up. All patients underwent neurological and radiological follow-up at 1 month post-treatment and every 2 months thereafter. Gadolinium-enhanced MRI was performed at these visits. Each patient also maintained follow-up with their medical oncologists.

Results

Between January 2006 and February 2013, 8 patients with 20 lesions were treated with SRS for single or oligo brain metastases. The mean age was 61 years (range, 41-78 years) and the median Karnofsky Performance Status score was 70. There were no metastatic cervical cancer patients in this cohort. While 1 patient presented with metastatic endometrial cancer, the remainder presented with metastatic ovarian cancer. Other potential, more common, primary sites (including co-existing lung or breast cancer) were ruled out by full staging scans. All patients had previously received systemic therapy and 1 patient had undergone whole brain radiation therapy (WBRT) 5 years earlier. While there were 11 treatment sessions for solitary lesions, 2 patients had 2 lesions each treated in 1 session and 1 patient had 5 lesions treated in 1 session. A total of 3 patients underwent a surgical

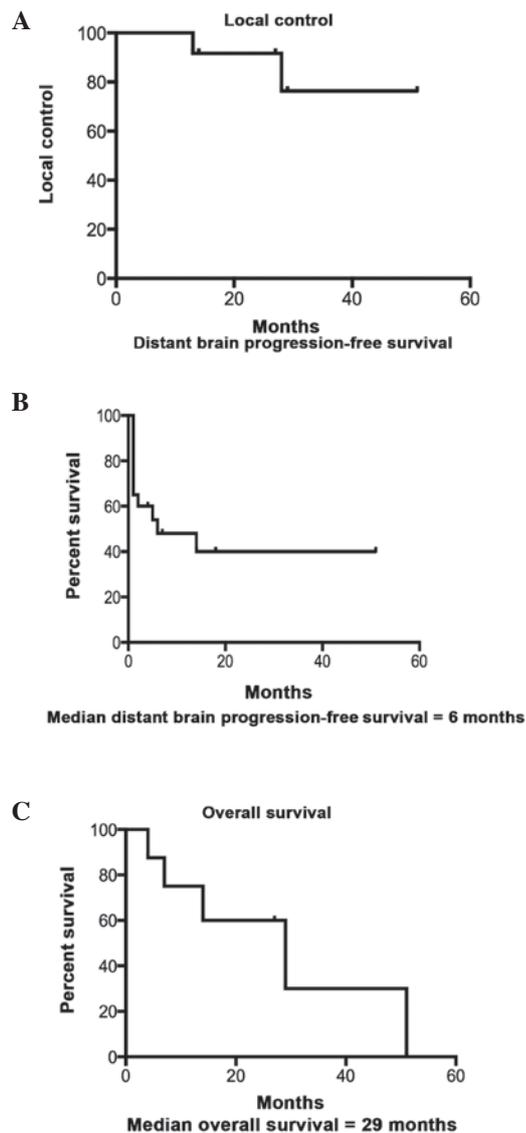


Figure 2. Kaplan-Meier actuarial estimates for (A) local control, (B) distant brain progression-free survival and (C) overall survival.

resection and 1 patient was provided with re-irradiation twice. A total of 11 lesions were infratentorial, including 2 in the cerebellopontine angle.

Local recurrence occurred and was re-irradiated twice in the cerebellum of the same patient, which eventually resulted in local control at the last follow-up. There were no other local failures. A total of 6 patients otherwise demonstrated treatment failure by exhibiting metastatic disease in the rest of the brain and therefore required repeat SRS. The 1-, 2- and 3-year actuarial local control rate was 91, 76 and 76%, respectively. There were 6 distant failures in 4 patients (2 patients demonstrated failures in the distant non-treated brain twice); salvage WBRT was administered to 1 patient for leptomeningeal failure, posterior fossa radiotherapy was administered to 1 patient and the other patients received further SRS. The median distant brain progression-free survival time was 6 months. The median overall survival time in this population was 29 months. The Kaplan-Meier survival curves for local control, distant brain progression-free survival and overall survival are shown in Fig. 2.

Discussion

Brain metastases from gynecological cancers, particularly endometrial and ovarian cancers, are extremely rare (4,18), hence, there are no strong guidelines for their management (19,20). Local therapy with SRS for smaller lesions and surgery for symptomatic space occupying lesions, with or without WBRT, has been the standard treatment. The management of oligometastatic brain disease in general is controversial and there is an increasing trend to use SRS in this setting. This is partially driven by worries of neurocognitive effects following WBRT (21). By contrast, in patients with widespread metastasis or leptomeningeal disease, WBRT remains the standard of care. In the present study, it was shown that patients with brain metastases from gynecological cancers, particularly ovarian cancers, can live a long time and that WBRT-sparing therapies such as SRS may be appropriate. SRS provides excellent local control and can be successfully used for salvage therapy, with limited recurrences.

With successful systemic therapy, patients with gynecological cancers may live for a long period of time (11-13). Prolonged survival rendered by effective modern systemic therapy may have led to the presumptive increase in the detection of brain metastasis (14-17) due to the inability of systemic therapy to breach the blood brain barrier (10). Randomized trials have shown no survival improvements with the addition of WBRT to surgery or radiation (22,23) for brain metastasis in general. In fact, avoiding WBRT can preserve or improve neurocognitive outcomes without the expense of decreased survival (21). While long-term neurocognitive sequelae remain a concern in all patients with limited brain metastasis, it becomes particularly relevant in this group of patients who survive longer. The median overall survival time of 29 months in the present study validates this hypothesis. Other groups have reported similar overall survival times in such patients. Kastritsis *et al* (10) reported long-term survivors, and Anupol *et al* (24) reported a mean survival time of 22 months in patients with brain metastasis from ovarian cancer. Similarly other studies have reported excellent local control and survival following SRS for endometrial cancer (25,26). By contrast, patients with brain metastasis from cervical cancer appear to do relatively poorly (6,27-29). This could reflect the inherent poor biological behavior of squamous cervical cancer.

Tumor markers are often unreliable in screening for brain metastasis (30), but cancer antigen 125 elevation can occasionally precede the clinical detection of brain metastasis (24), and elevated marker levels with no other signs of metastasis in the presence of neurological symptoms should arouse suspicion.

Surgical resection when appropriate (31) plus WBRT has been previously used in patients with brain metastasis from gynecological malignancies. Certain studies have reported improved outcomes with multimodality treatments that include surgical resection (8,14). However, the majority of series have used WBRT to treat these patients. In fact, the Hellenic Oncology Group reported poor outcomes primarily with the use of WBRT or supportive care (32).

Prior studies have reported the use of SRS in patients with brain metastasis from gynecological malignancies. (27,33-35). Improved outcomes after SRS compared with WBRT (25,33,35) could reflect selection bias. Patients with isolated or

limited CNS disease, controlled systemic disease and reasonable performance status appear to do well overall (19,24), and are those who could potentially benefit from WBRT-sparing approaches such as SRS. In the present study, it was shown that patients with a reasonable performance status and controlled systemic disease can achieve excellent local control rates and achieve long overall survival times with SRS treatment alone. This is particularly true due to the high efficacy of SRS for isolated brain relapses, with WBRT reserved for widespread and leptomeningeal metastases.

In conclusion, brain metastasis from gynecological malignancies is rare. Systemic therapy is effective in patients with metastatic cancer of the female genital tract, who can subsequently survive for a long period of time. In this setting, when these patients present with limited brain metastasis, surgery (when appropriate) and/or SRS is effective in controlling the brain disease.

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