BRAIN METASTASIS FROM UTERINE MALIGNANCIES: TREATMENT MODALITIES AND PROGNOSTIC FACTORS

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ABSTRACT

Isolated brain metastases from gynecologic malignancies are unusual. Advances in therapeutic modalities including surgery, whole brain radiotherapy, stereotactic radiosurgery and chemotherapy improved survival and quality of life in this population. The therapeutic decision is based on patients' specific prognostic factors. We report three cases of isolated brain metastases from gynecologic cancers and discuss treatment modalities in the light of a literature review.

KEYWORDS brain metastasis, gynecologic malignancies, brain surgery, stereotactic radiosurgery, whole brain radiotherapy

Introduction

Brain metastases (BM) from gynecologic malignancies are uncommon. They usually occur in patients with disseminated disease. As advances in therapeutic options improved survival in selected patients, the issue of patient selection gained importance. Treatment decision is based on patients' specific prognostic factors defining patients that may be eligible for aggressive local therapeutics. We report 3 cases of isolated BM from gynecologic malignancies and discuss therapeutic options and prognostic factors for overall patient survival.

Case Report 1

Forty-nine-years-old woman with no medical history who complained eight months before from spontaneous vaginal bleeding. Physical examination, pelvic MRI chest and abdominal CT concluded in a uterine cervix cancer stage FIGO IIIb. Biopsy confirmed the diagnosis of squamous cell carcinoma moderately differentiated. She underwent external radiotherapy at a dose of 46 Gy in 23 fractionation associated to weekly cisplatin based chemotherapy followed by intracavity brachytherapy (4x7 Gy) making a total irradiation duration of 56 days. Eleven months later, she presented with a progressive weakness of the left hemibody, dysarthria, and headache. Brain MRI showed a unique temporal lesion associated with a perilesional edema evocating a secondary tumor (figure 1). An exhaustive workup revealed no other abnormalities. She underwent a stereotactic biopsy; pathological examination revealed an undifferentiated squamous cell carcinoma and along with her medical history, confirmed an isolated brain metastasis of cervix carcinoma. The patient underwent metastasectomy followed by radiotherapy to the whole brain at a dose of 30 Gy in 10 fractions. She is free of symptoms 30 months later.

Case report 2

This is a 62-years-old postmenopausal patient, treated in 2009 for adenocarcinoma of the endometrium revealed by vaginal bleeding and an exophytic endometrial lesion at hysteroscopy. The patient received total hysterectomy with bilateral adnexectomy and pelvic lymph node dissection. Pathological examination showed endometrioid adenocarcinoma moderately differentiated infiltrating less than 50% of the thickness of the myometrium, WHO grade 3. Lymph node dissection showed no metastatic nodes

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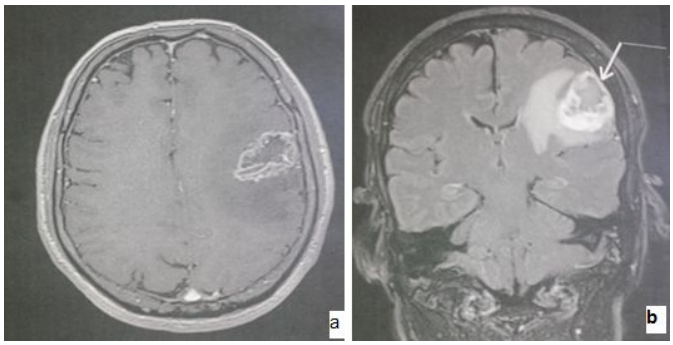

Figure 1: Left parietal brain metastasis with dual component cystic and fleshy with peritumoral edema on T1 MRI a- axial T1 MRI b- coronal T2 MRI.

(14N- / 14 N). The patient was classified stage IA / according to FIGO classification 2009. Adjuvant external radiotherapy to the tumor bed at a dose of 46 Gy (2 Gy / fraction) followed by vaginal Brachytherapy at a dose of 2 * 7Gy indicated. Two years after the end of treatment, the patient presented severe headaches, vomiting, and ataxia. Brain MRI confirmed the presence of one brain stem lesion evoking a secondary location (figure 2). The patient underwent a Stereotactic biopsy, histological study and chemical staining was for a cerebral metastasis of a poorly differentiated adenocarcinoma with positive hormonal receptors. Chest, abdominal and pelvic computed tomography showed no abnormality. The patient received external radiotherapy to the whole brain at a dose of 30Gy (3 Gy / fraction) delivered by two opposed lateral 6 MV X-ray beams, followed by six courses of carboplatin and docetaxel-based chemotherapy. The patient is symptom-free 18 months after treatment.

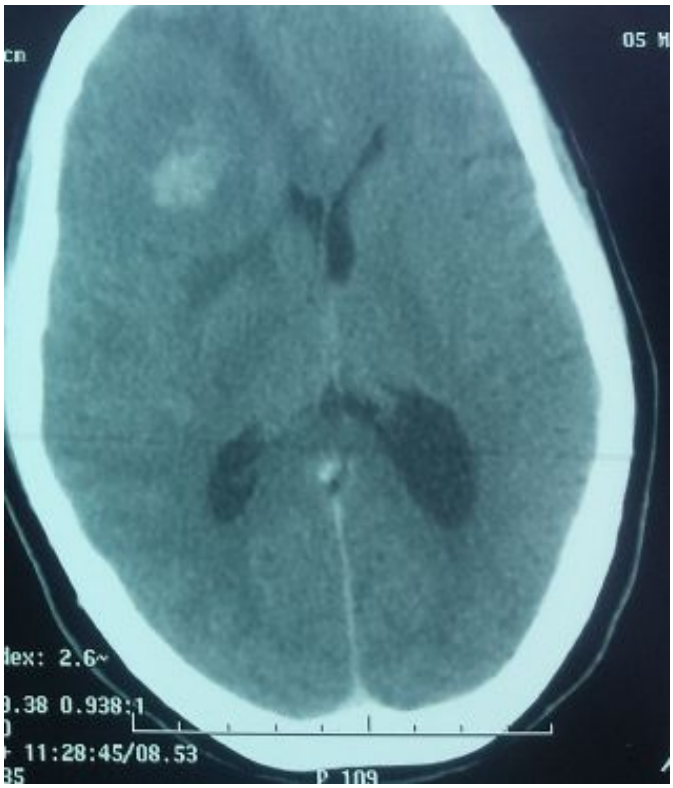

Figure 2: Axial T2 and coronal T1 MRI showing a brainstem metastasis with important perilesional edema.

Case report 3

A fifty-five-years-old woman with no particular history who complained suddenly from hemi-body weakness. Brain CT showed a frontoparietal lesion associated with a substantial edema (figure 3). She underwent a stereotactic biopsy histological examination with chemical staining revealed a brain metastasis from a neuroendocrine tumor (positivity to CD56 antibodies). Chest, abdominal and pelvic computed tomography showed an endometrial thickness confirmed at pelvic ultrasound with no other metastatic site. A curettage biopsy confirmed a primary neuroendocrine tumor of the endometrium. She underwent SRS followed by whole brain radiation therapy at a dose of 30 Gy in 10 fractions and 14 days. Then she received a combination of cisplatin and etoposide-based chemotherapy. She died after the third course of neurologic progression.

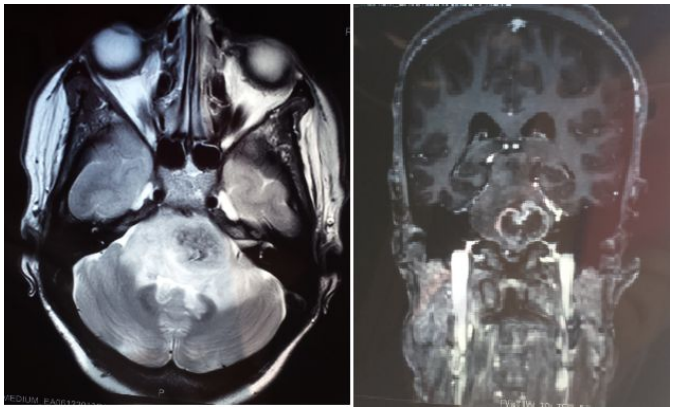

Figure 3: Right fronto- parietal brain metastasis enhanced after the injection of contrast material associated with peritumoral edema and mass effect on CT scan.

Discussion

Brain metastases (BM) are the most common brain malignancies in adults. Half of BM are originated from lung cancer, 15–20% from breast cancer, and 5–10% from melanoma. [1–2] BM from gynecologic cancers apart from choriocarcinoma are rare and usually associated with disseminated disease. [3–4] BM from cervical, endometrial and ovarian cancer account for 0.3–0.9%, 0.4–1.2% and 0.3–2.2%, respectively. [5] Lesions follow a hematogenous spread pattern to the lungs, then to the brain through carotid arteries. Many patients have simultaneous pulmonary metastasis that may be a predisposing factor for BM. [6] Because of their rarity, no screening program is addressed, and patients usually present with symptoms. Presenting symptoms are similar to other expansive intracranial processes such as a headache, seizure, and neurologic impairment.

Several treatment modalities are so far available including surgery, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) alone or associated to WBRT. Corticosteroidtherapy (dexamethasone or methylprednisolone) is always recommended to improve edema and neurologic symptoms with starting doses of 4–8 mg/day and 16 mg/day for patients with signs of increased intracranial pressure. [7] Therapeutic decision in such a heterogeneous population is discussed based on patients' specific prognostic factors setting an aim of treatment that might be symptom palliation or survival improvement to select patients that might benefit from local aggressive therapies. [8]

Surgery can provide immediate symptom relief. Traditionally, resection followed by WBRT was considered the standard treatment for patients with isolated (limited to the brain only) and single (solitary) BM. A multimodal treatment associating brain surgery to WBRT prolonged overall survival (40 weeks) compared to radiotherapy alone (15 weeks) ($p = 0.0001$) $p<0.01$ in patchell and all's randomized study. [9] It improved functional independence (40 vs. 15 weeks) ($p<0.1$) and time to local failure compared to radiotherapy alone in Three phase III trials. [9-10-11] The benefit was mainly obtained in a subgroup of patients with stable disease and good performance status. [12] Cormio et al. [13] reported a series of 10 patients with BM of endometrial carcinoma treated either by craniotomy alone, craniotomy followed by WBRT, WBRT alone, or steroids alone. Survival improved in the surgery + WBRT group, and the authors concluded that surgery followed by WBRT is considered the best therapeutic option in patients with solitary BM and controlled systemic disease. In our first patient, as she had a controlled primary and a good performance status (PS), she underwent craniotomy followed by WBRT. She is alive with no evidence of disease 30 months after completion of treatment.

In the case of multiple BM, surgery is reserved to symptom palliation or to provide biopsy samples. [14-15] Stereotactic radiosurgery is a less invasive alternative to conventional surgery in patients with three lesions or less and who may not be craniotomy candidates for the tumor location or medical history. Stereotactic radiosurgery (SRS) offers the ability to treat tumors with relative sparing of normal brain tissue in a single fraction and therefore, patients treated with SRS alone would experience less cognitive and constitutional side effects. Repeat SRS may be performed for new lesions to avoid or delay WBRT for as long as possible.

SRS achieves same outcomes as surgery, especially in small lesions. Although there is no randomized trial comparing surgery to SRS. The use of SRS is well described for brain metastases in primary lung, breast, colon, and other cancers. Before 2001, SRS was not yet introduced in the treatment of BM from gynecologic cancers. Petru et al. [16] were the first to describe in 2001 two patients with BM from endometrial carcinoma treated with SRS. One of these two patients died 15 months after diagnosis of BM; the other patient was still alive with no evidence of progression 171 months after SRS.

In 2008, Monaco et al. [17] reported the outcomes of six patients with BM from endometrial carcinoma and 21 patients with ovarian carcinoma treated with SRS. The median survival was seven months from diagnosis. At imaging studies, two patients (7.4%) developed new lesions after SRS and all other patients were controlled. The authors concluded that SRS is a good choice for the treatment of BM as it provides local tumor control with limited morbidity. Menedez et al. [18] evaluated the local control of gamma knife stereotactic radiosurgery in 14 patients with brain metastases from primary endometrial, ovarian, and cervical cancer. From 74 tumors, 63 showed no radiographic evidence of progression. In six patients, further treatment with GKSRS was necessary for progressive or new metastatic disease. The authors concluded that GKSRS was efficacious in controlling uncommon BM.

It seems that total treated volume is the best selection criterion than number of lesions. An amount less than 5 to 10 cc is associated with a better survival as demonstrated in a multivariate analysis of 205 patients with 4 or more lesions [19]. Similar studies showed that number of lesions did not impact survival or time to local failure suggesting that patients with multiple lesions but small treated volume may be candidates to SRS. [20-21] There is no established consensus regarding the maximum number of BM to treat with SRS alone. Prospective surveys comparing SRS alone to SRS plus WBRT for five BM and more are still needed to address this issue [22-23]. SRS boost in addition to WBRT or after metastasectomy improves local control. SRS after WBRT significantly improved survival in patients with single BM in two randomized, controlled trials and a meta-analysis (6.5 vs. 4.9 months). [24-25-26] This benefit was not observed in patients with multiple metastases. However, SRS boost in these patients prolonged time to local failure. In the situation of relapse after WBRT, SRS demonstrates high rates of local control in patients with good PS and stable disease. [27]

Whole-brain radiation therapy (WBRT) can reduce radiographically evident metastases and treat presumed micrometastatic deposits at distant intracranial locations. WBRT as primary therapy continues to be the standard of care in BM when surgery or SRS are not possible or as additional therapy to prevent brain recurrence as brain failure after surgery in and outside the original site are 46% and 70% respectively [28], suggesting that omission of the upfront radiation therapy to the whole brain should be taken with caution.

In fact, in patients who underwent SRS as primary treatment, it is discussed whether the addition of WBRT may improve survival and local tumor control in selected patients. Three randomized trials from Japan, Europe, and the MD Anderson Cancer Center tried to address this issue. [29-30-31] The first randomized trial comparing SRS alone to SRS plus WBRT was a Japanese multi-institutional Phase III study (JROSG 99-1) that enrolled 132 patients with 1-4 lesions [29-32]. Results showed that addition of WBRT reduced 1-year intracranial relapse rates and neurologic mortality (17% versus 76% $p<0.001$) but did not influence median survival.

Radiation therapy should be started early before systemic therapies especially in the presence of life-threatening lesions as there is no evidence that delaying chemotherapy impacts survival. On the other hand, in patients with a predicted survival that could extend six months, whole brain radiotherapy with hippocampal sparing techniques should be considered to reduce neurocognitive sequelae. For patients with an inaccessible tumor to surgery or extensive systemic disease, WBRT is the leading primary therapy. A dose of 30 Gy in 10 fractions continues to be the standard. A small fractionation scheme (20 Gy in 5 fractions) can be considered in patients with disseminated disease and chemotherapy-refractory disease.

Systemic therapy indicated in case of the disseminated disease. Hormone therapy in metastatic endometrial cancer is indicated in the presence of a well-differentiated adenocarcinoma, positive hormone receptors or a low-performance status and no chemotherapy. Prognosis of BM from gynecologic malignancies remains weak especially in patients with disseminated disease. In a literature review by Piura et al. that examined published series until December 2011, Reported survival that time ranged from 0.1 to 171 months with a median of 5 months. [33]

Treatment modality significantly impacts overall survival as reported by Chura et al. [34] who reviewed 20 patients with BM from endometrial carcinoma treated at Women's Cancer Center in Minneapolis, USA and showed that multimodal therapy associating (WBRT + craniotomy, WBRT + craniotomy + chemotherapy, WBRT + SRS, WBRT + chemotherapy) linked with longer survival. Same results were reported by Mahmoud

et al. in 2002. [28]

Through a literature review of BM from cervical carcinoma about 100 cases documented in the literature until the paper was written, Piura et al. reported that multimodal therapy achieved a better outcome (craniotomy followed by WBRT vs. craniotomy alone or WBRT alone). The best survival was achieved in patients undergoing SRS either alone or in combination with other treatment modality, although based on a small number of patients. [35]

In a multi-institutional retrospective study evaluating prognostic factors associated with overall survival in 139 patients [36], young age, Karnofsky performance >70, histology of primary, controlled primary site, and absence of extracranial extension are independent factors related to survival. Using combined modality treatment associating cranial surgery, cranial radiotherapy, and systemic therapy were independent favorable prognostic factors. Also, the presence of single BM is associated with improved survival (17 months vs. three months in multiple BM, p=0.017). [32]

In our patients, multimodal treatment did result in a neurologic disease control and a good survival time in the two first patients (30 and 18 months). In our last patient who had an endometrial neuroendocrine tumor, survival did not exceed three months after diagnosis of BM, which enhances histological type as a prognostic factor on its own.

Conclusion

Although brain metastasis from gynecologic malignancies is rare, it should be investigated in patients with neurologic symptoms. Consistent with previous researchers, our case reports highlighted the traditional prognostic factors of solid tumors based on; patients best are selected for aggressive local therapies. Multimodality treatment associating WBRT to surgery or SRS is associated with better outcomes for patients with a good performance status and limited brain metastases.

Disclosure Statement

There were no financial support or relationships between the authors and any organization or professional bodies that could pose any conflict of interests.

Competing Interests

Written informed consent obtained from the patient for publication of this case report and any accompanying images.

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