



Primary brain metastases of endometrial cancer: A report of 18 cases and review of the literature



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HIGHLIGHTS

- Brain metastases from endometrial cancer occur in <1% of cases.
- In patients with single lesions without extracerebral spread, surgery and brain radiotherapy is associated with encouraging oncologic outcomes.

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ABSTRACT

Objective. To present a series of brain metastases from endometrial cancer (EC) and describe a comprehensive review of the literature.

Methods. We retrospectively reviewed medical records of 1) patients with cerebral dissemination of EC treated at Mayo Clinic from 1984 to 2001 and 2) all patients referred for treatment of primary brain metastases after primary treatment for EC elsewhere. We also reviewed published case reports and case series describing cerebral spread of EC.

Results. Among the 1632 patients treated at Mayo, 14 (0.86%) had primary brain dissemination; 4 additional referral cases were identified (total, 18 patients). In 2 cases (11.1%), diagnosis of brain metastases was made at presentation of EC; in the others, median time to development of brain metastasis was 5 (range, 1–57) months. Median survival was 57 (range, 7–118) months in patients with single cerebral metastases and no extracerebral involvement ($n = 6$); for the remaining 12 patients, median survival was 4 (range, 0–28) months. Among the 6 patients with single brain metastases, complete surgical excision was possible in 5; in that group, the overall survival was 64 (range, 12–118) months. We identified 98 cases of brain metastases of EC in the literature: 58 were primary cerebral metastases. Overall survival after brain dissemination was significantly higher in patients with a single metastasis without other localization and receiving multimodal treatment including surgery and whole-brain radiotherapy.

Conclusions. Single primary brain metastases without extracerebral spread seem to have a relatively favorable prognosis. Aggressive multimodal treatment may include surgery and brain radiation.

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1. Introduction

For patients with endometrial cancer (EC), brain metastases are a rare occurrence. With fewer than 100 cases described in the literature, some authors have defined EC as a “neurophobic” malignancy [1]. Unfortunately, the available data on brain metastases of EC are derived from case reports or small case series that also include carcinosarcomas

Abbreviations: EC, endometrial cancer; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics).

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(which may represent a different entity, with respect to EC). These reports combined data of patients with cerebral dissemination as the first site of recurrent EC with those of women with brain metastasis as a second or third site of recurrence, after development of metastasis at different anatomic sites [2,3]. Consequently, no clear conclusions can be drawn from the literature regarding the characteristics and optimal management of patients with primary cerebral dissemination of EC.

Of note, a recent review of the literature by Piura and Piura [3] showed that median overall survival after diagnosis of brain metastasis is only 5 months. Again, although Piura and Piura's analysis is thorough and comprehensive, it is flawed by the inclusion of carcinosarcoma cases, the mixture of primary and secondary brain metastases (i.e., metastases to the cerebrum as the first vs subsequent site of recurrence), and the inclusion of a series of patients with cerebral dissemination of EC but no specific information about patient characteristics and outcomes [4].

To overcome the confusion existing in the literature regarding the real incidence and the possible predictors of survival after cerebral dissemination from EC, we reviewed and analyzed primary brain metastases (i.e., those discovered either at the time of presentation with EC or when the first site of recurrence was found) of patients treated at Mayo Clinic. We also comprehensively reviewed all reports published on this topic and clearly distinguished between primary cerebral dissemination and secondary relapses.

2. Materials and methods

Mayo Clinic Institutional Review Board approval was obtained for this study, and all patients provided written informed consent for the collection of data for research purposes.

2.1. Patient selection and characterization

A total of 1632 patients affected by EC were surgically treated at Mayo Clinic (Rochester, Minnesota) from January 1, 1984, through December 31, 2001. Primary cerebral metastases were defined as all cases of EC metastatic to the brain, identified either at presentation of disease or as the primary anatomic site of recurrence (alone or with other locations). Secondary brain metastases were defined as cerebral recurrence of endometrial cancer after 1 or more relapses at different anatomic sites were diagnosed. Brain recurrence was diagnosed on the basis of signs, symptoms, imaging findings, and surgical or histologic information documented in the health record. We also included patients who underwent primary treatment for EC elsewhere but were then referred to Mayo Clinic during the study period and received therapy for primary brain metastases. EC was staged according to the 2009 FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) staging system [5]. Architectural grading (i.e., the degree of glandular differentiation) was based on FIGO guidelines. Descriptions of tumor characteristics were abstracted from the original pathology reports. A pathologist (G.L.K.) retrospectively reviewed all pathology slides (hematoxylin-eosin stain) of primary tumors to confirm FIGO grade and histologic subtype. Type I histology was defined as endometrioid adenocarcinoma or adenosquamous subtype; type II histology included papillary or serous, tubulopapillary, clear cells, anaplastic and undifferentiated cancers, and adenocarcinomas with neuroendocrine differentiation. Patients with uterine sarcomas, carcinosarcomas, or synchronous primary cancers were excluded.

Brain scans of all study patients were reviewed by a senior radiologist (J.M.M.), who confirmed the diagnosis of brain relapse made at imaging. Brain recurrences were categorized as either having concomitant recurrence with other organ sites or being an isolated recurrence in one or more sites of the brain. Cerebral metastases were also classified as either single or multiple brain lesions.

Follow-up data were obtained from electronic health records. For patients with insufficient available data, we systematically sought

death certificates and contacted the patients' family physicians (interviewed by letter or telephone) to obtain complete information. Patients were censored if they were alive at last follow-up (with or without disease) or if they had died of causes unrelated to EC.

2.2. Literature review

We systematically searched the PubMed database for reports published from January 1, 1950, through August 31, 2015, using the terms "brain metast*"; "brain relapse"; "brain recurrence"; "cerebral dissemination" AND "endometrial cancer"; "uterine cancer". We identified all case reports and series describing subjects with brain metastases of EC. We also manually searched reference lists from each article of interest to capture other potentially relevant publications that were not identified by the electronic search. We considered papers published in English, French, Spanish, or Italian.

2.3. Statistical analysis

Statistical analysis was performed using JMP statistical software (version 4.0.4; SAS Institute, Inc) and SPSS (version 21.0 for Windows; SPSS Inc). The *t*-test and Mann-Whitney *U* test were used to compare continuous parametric and nonparametric variables, respectively. Fisher exact test, Kaplan-Meier product-limit method, and log-rank test also were used as appropriate. All tests were 2-tailed. Statistical significance was defined as $P < 0.05$.

To identify possible independent predictors of survival after diagnosis of primary brain metastases, we considered data from all cases identified by the literature search and added the findings from our series of patients treated at Mayo Clinic for primary brain metastasis. Survival analysis was accomplished by plotting Kaplan-Meier curves, and curves were compared by using the log-rank (Mantel-Cox) test. The log-rank test was used for univariate analysis of variables that potentially affected survival. All variables that suggested a possible association with survival ($P \leq 0.10$) were included in a multiple logistic regression analysis model (with survival >1 year after brain metastasis [yes/no] modeled as the dependent variable) and in a linear logistic regression model to identify factors independently associated with prognosis.

3. Results

Primary brain metastases were diagnosed in 14 of 1632 patients with EC (0.86%) treated at Mayo Clinic during the study period. Four additional patients were referred to Mayo after initial treatment at other institutions. Of the 18 patients included in this study, 9 (50%) had a single metastasis in the brain, 2 (11.1%) had 2 metastases, 1 (5.6%) had 3 metastases, and 6 (33.3%) had >3 metastases. The most brain metastases observed in a single patient was 17. Patient characteristics are summarized in Table 1 and are described in detail in Table 2. A multidisciplinary team with expertise in medical and surgical oncology and treatment of cerebral secondary tumors defined therapeutic strategies for patients with brain relapses.

In 2 patients (11.1%), the discovery of brain metastases was made at the time of initial diagnosis of EC. In the remaining 16 (88.9%), the median time to diagnosis of brain metastasis was 5 months (range, 1–57 months). The diagnosis of primary brain metastasis was made within 5 years after the initial diagnosis of EC in all patients, and it was diagnosed within 2 years in 16 (88.9%). Cerebral relapse occurred in 2 women (40 and 57 months after diagnosis of EC).

Metastatic lesions were evenly distributed in the brain (Table 1). The supratentorial cerebrum was the most commonly involved region ($n = 16$ [88.9%]). The cerebral lobes were not a preferential site of metastasis.

No cases were diagnosed incidentally; all 18 patients had symptomatic brain metastases, and diagnosis was made on the basis of radiologic findings. The most common concerns were upper or lower limb weakness or paresis ($n = 9$ [50%]) and refractory headache ($n = 6$ [33.3%]).

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