

BRAIN METASTASIS OF OVARIAN EPITHELIAL CARCINOMA

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Ovarian cancer is the seventh most common cancer and the fifth leading cause of cancer death in the world, after lung and bronchial cancers, and breast, colorectal and pancreatic cancers. Ovarian cancer causes more deaths than any other cancer of the female reproductive system. Brain metastases resulting from primary ovarian cancer are uncommon [1]. However, recent studies have suggested an increased incidence of brain metastases in patients with primary ovarian cancer [2–4]. Surgery, irradiation, and chemotherapy can all be used to prolong patient survival, although the prognosis remains poor [4]. McMeekin et al [5] studied the survival of 104 ovarian cancer patients with metastatic brain disease following a combination of surgery, irradiation, and/or chemotherapy. Their report indicated a median survival of 6 months for these patients, regardless of the treatment modality [5]. Some investigators have reported relatively successful efforts in prolonging the life of these metastatic patients. Gabriele et al reported a mean survival of 17 months in a group of 23 ovarian cancer patients with solitary brain metastases treated with surgery and radiotherapy [6]. The survival of ovarian cancer patients with metastatic disease treated with irradiation was around 2 years [5,7]. Systemic chemotherapy has also proven effective for the treatment of brain metastases [1,7].

A 58-year-old Taiwanese woman was originally referred to our gynecologic oncology clinic for treatment of an ovarian epithelial carcinoma in May 2005. She presented with increased abdominal girth and poor appetite. Her preoperative serum CA-125 level was 4,491 U/mL. She underwent laparotomy with optimal debulking surgery (*en bloc* total abdominal hysterectomy

and bilateral salpingo-oophorectomy, and cavitron ultrasonic surgical aspirator debulking from the peritoneal surfaces). The pathology revealed a poorly differentiated stage IIIc ovarian serous adenocarcinoma (Figure 1) with metastasis to the omentum, appendix, paraortic and pelvic lymph nodes. The patient subsequently received six courses of paclitaxel and carboplatin, commencing in June 2005. Her CA-125 level fell to 12.7 U/mL in November 2005, and complete clinical and surgical remission was achieved. Another 12 courses of maintenance paclitaxel chemotherapy were administered thereafter, and her serum CA-125 level ranged from 12 to 15 U/mL until November 2006. In May 2007, she presented with intermittent headaches, nausea, cognitive dysfunction, gait ataxia, and urinary and fecal incontinence, resulting in consultation with a neurologist. There was no weakness, syncope or seizure history. A brain magnetic resonance imaging examination revealed a 5-cm mass in the left frontal lobe with a cystic component and irregular thick wall, and perifocal edema with compression of the left lateral ventricle, resulting in midline structures shifting to the right side (Figure 2). No other apparent lesions were noted in the abdomen, chest or spine. An elevated serum CA-125 level, as high

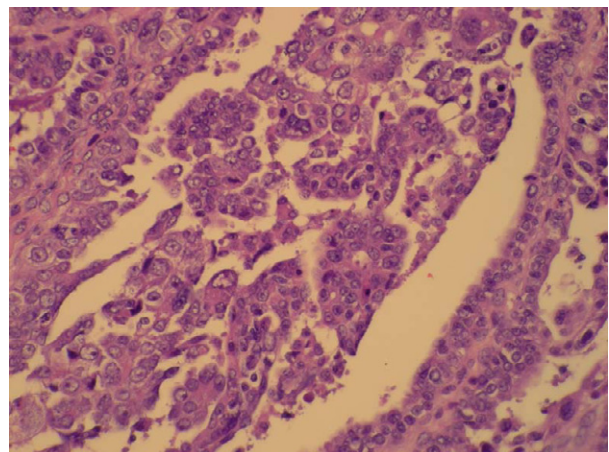


Figure 1. Pathologic report showed typical serous adenocarcinoma.



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as 331 U/mL, was also noted. Our patient underwent resection of the left frontal mass in May 2007. The pathology revealed metastatic adenocarcinoma consistent with the ovarian origin (Figure 3). She subsequently received adjuvant radiation therapy (5,000 cGy) to the tumor bed in 25 fractions, using the three-dimensional conformal technique, from June to August 2007, together with chemotherapy (carboplatin and doxorubicin). A magnetic resonance imaging scan in September 2007 was unremarkable, with no evidence of recurrent malignancy (Figure 4). The patient's serum CA-125 remained normal, and she continued to be a pleasant and active individual.

The cases of ovarian cancer with brain metastasis reported in the English literature are summarized in the Table. These cases had durable oncologic control; however, the rarity of this entity means that no prospective randomized studies aimed at determining the standard of care are currently available.

The use of optimal cytoreductive surgery to treat ovarian cancer that has developed into metastatic brain disease is not common, although some reports have suggested that its use may be increasing [2–4]. Few large-scale studies, however, have addressed the question of the best treatment strategy for these patients. Several published reports demonstrated that aggressive treatment might be effective in selected patients. The addition of radiation and chemotherapy to surgical resection of solitary brain metastases has been associated with durable control [1,4,7]. Rodriguez et al [8] reported a median survival of 20 months using this multidisciplinary approach. Surgery combined with cisplatin-based chemotherapy and stereotactic radiotherapy may prolong patient survival even further. Patients with solitary brain metastases are most likely to benefit from aggressive multimodality treatment. Cormio et al [1] reported a patient with grade IV ovarian carcinoma who developed brain metastases and survived for 30 months following chemotherapy with carboplatin, before eventually succumbing to recurrent pelvic disease.

The hematologic and lymphatic systems both provide common routes for metastasis of primary ovarian cancers to the brain. However, treatment does not differentiate between these two routes of cancer dissemination into the central nervous system. The application of chemotherapy to brain tumors has been limited by the inability of most chemotherapeutic agents to penetrate the blood–brain barrier. It has, however, been suggested that doxorubicin is strong candidate for chemotherapy of the central nervous system, because it is thought to have the ability to cross the blood–brain barrier. We attributed the isolated central nervous system metastasis in our patient to the inability of the chemotherapeutic

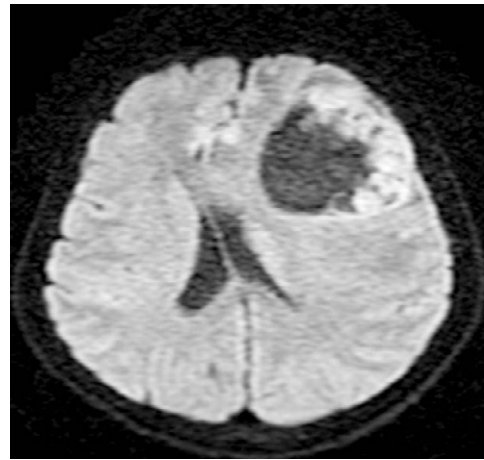


Figure 2. Solitary large tumor mass with irregular thick wall and a mainly cystic component (maximum diameter, 55 mm) was noted in the left frontal area and left frontal and ventricle with overt perifocal edema and compression.

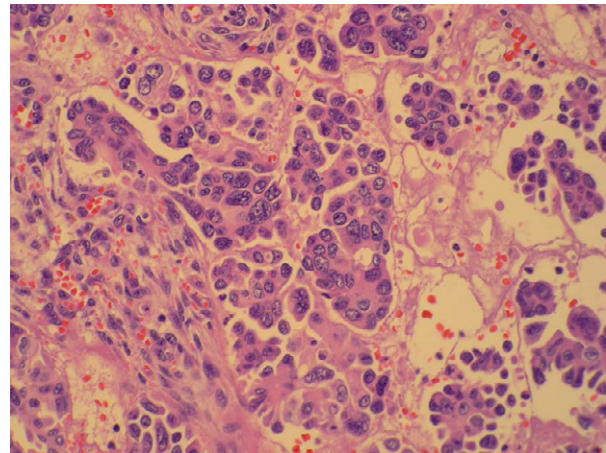


Figure 3. Histopathologic examination of the brain lesion revealed similar morphology to that of the primary ovarian serous adenocarcinoma.

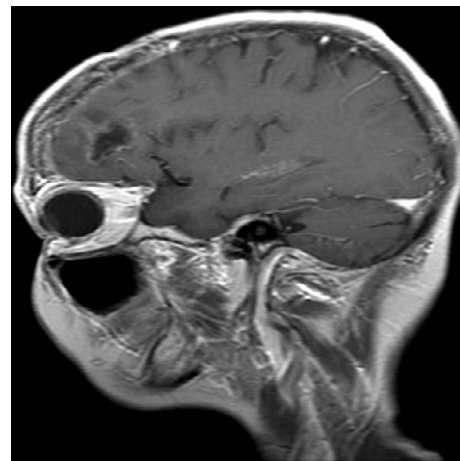


Figure 4. Brain magnetic resonance image 4 months after surgery showed no signs of recurrence. Some postoperative changes with bone defects and tissue loss in the left anterior frontal area were noted.

Table. Cases of ovarian cancer and brain metastasis in the English literature

Author	Stage	Histology	No. of cases	Age (yr)	Time to first disease relapse (mo)	Surgery to brain lesion	CT regimen	RT to brain	CA-125 at brain metastasis (U/mL)	Brain lesion (multiple or solitary)	Survival after relapse or follow-up duration (mo)
Cormio et al [1]	IV	Serous	1	49	7	No	Carboplatin	No	542	Multiple	30
Suzuki et al [12]	IIIc	Serous	1	50	32	Yes	Carboplatin + cisplatin	Yes	76	Solitary	57
Tay et al [13]	IIc-IVb	Endometrioid Serous Serous Clear cell	4	52.5 (mean)	26.5 (mean)	Yes (n=1)	Paclitaxel + carboplatin	Yes (n=2)	8.9 44 45 263	Multiple (n=3) Solitary (n=1)	16.5 (mean)
Kastritis et al [14]	IIIc & IV	Serous (n=6) Others (n=2)	8	59 (mean)	17.2 (mean)	Yes (n=1)	Paclitaxel-based	Yes (n=7)	Elevated in 2 cases	Multiple (n=4) Solitary (n=4)	22.5 (mean)
Anupol et al [15]	IIIc & IV	Serous (n=14) MMMT (n=1)	15	NM	22 (mean)	Yes (n=5)	Yes (n=9)	Yes (n=13)	51 (mean)	Multiple (n=7) Solitary (n=7)	20 (mean)
Chen et al [11]	III & IV (n=18) Ic (n=1)	Adenocarcinoma (n=9) Serous papillary (n=7) Other (n=3)	19	51 (mean)	36 (mean)	Yes (n=9)	NM	NM	NM	Multiple (n=12) Solitary (n=7)	33.7
D'Andrea et al [16]	II	Serous epithelial papillary adenocarcinoma	11	60.3 (mean)	21 (mean)	Yes	Yes	Yes	NM	Solitary	28 (mean)

CT = chemotherapy; RT = radiotherapy; MMMT = malignant mixed müllerian tumor; NM = not mentioned.

agents used for her primary ovarian cancer to penetrate the blood–brain barrier. A recent study reported the use of intra-arterial chemotherapy with or without blood–brain barrier disruption, and demonstrated excellent outcomes in patients with ovarian cancer metastases to the brain [9]. Many chemotherapeutic agents (e.g. carboplatin) were unable to permeate the blood–brain barrier, and were thus unable to protect patients from the subsequent development of brain metastases [10]. The solitary brain metastasis in our patient may have contributed to her relatively protracted survival, compared with patients with multiple lesions [7].

Chen et al [11] investigated 19 cases of ovarian carcinoma with brain metastases and concluded that the Radiation Therapy Oncology Group recursive partitioning analysis prognostic classification system was valid in this patient group. They also identified multiple brain lesions and the absence of surgical resection as the two main prognostic factors predictive of a poor outcome.

In conclusion, recurrence of ovarian cancer in the brain is an extremely rare event. Serum CA-125 measurement has a poor predictive value for brain metastasis, compared with other metastases. Diagnostic examinations, such as computed tomography or magnetic resonance imaging, are often not arranged until symptoms develop. A standard management program for these cases is yet to be determined, and the establishment of multicenter collaborative studies is warranted. When possible, aggressive treatment with surgery and/or irradiation therapy, as well as chemotherapy, is recommended in this subgroup of patients with recurrent and metastatic ovarian cancer.

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