Brain Recurrences in Patients with Ovarian Cancer: Report of 12 Cases and Review of the Literature

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Abstract. *The aim of the investigation was to assess 12 cases of brain recurrences among ovarian cancer patients who had undergone surgery followed by platinum-based chemotherapy. Brain lesions were the first recurrence in 4 (33%) patients, the second recurrence in 7 (58%), and the fourth recurrence in one patient. The median time from ovarian cancer diagnosis to brain metastasis detection was 33.5 months (range, 13.5-86.5 months), brain metastases were multiple in 6 (50%) cases, and extra-cranial disease was present in 7 (58%) cases. Brain recurrence was symptomatic in 10 patients and the clinical presentation included impaired deambulation, extremity weakness, seizure, headache, nausea/vomiting and visual disturbance. Out of the 6 patients with single brain metastases, one underwent surgery, one had surgical excision followed by whole brain irradiation, 3 patients received stereotactic radiotherapy (followed by chemotherapy for coexistent extra-abdominal recurrence in one), and one had only symptomatic treatment. Out of the 6 patients with multiple brain metastases, four received whole brain irradiation (followed by chemotherapy for concomitant extra-cranial recurrence in one case), one patient had gamma-knife irradiation of three cerebral lesions (followed by chemotherapy for concurrent abdominal recurrence), and one patient had only symptomatic treatment. The median overall survival from diagnosis of brain metastasis was 8.3 months (range, 1-28 months), and it was not related to the number of brain metastases (multiple versus single), presence or absence of extra-cranial disease, or interval between ovarian cancer diagnosis and brain metastasis detection (<33.5 months versus ≥33.5 months). In conclusion, brain metastasis from ovarian cancer can represent a late manifestation of the disease, associated with a very poor prognosis.*

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Key Words: Ovarian cancer, brain metastasis.

Brain metastases from ovarian cancer are an uncommon and often late manifestation of the disease, with an incidence range from 0.2% to 11.6% in different series in the literature (1-9). However, the estimates of brain involvement may be considered reliable only in large series based on records of hundreds of treated patients (10). Collected data from 13 articles including 22,240 ovarian cancer patients have revealed 219 cases of brain metastases, for an overall incidence of 1.01% (1, 6, 7, 9, 11-20). Some authors have reported a small, but significant, increase in the incidence of brain involvement over the last 20 years, probably due to better primary control of intra-abdominal disease with cytoreductive surgery and aggressive chemotherapy leading to a longer survival and allowing neoplastic cells to seed and grow at distant sites (1, 5, 6, 8, 9, 12, 16, 20). Chemotherapeutic agents cross the blood–brain barrier poorly, therefore the brain may be a pharmacological sanctuary from systemic treatment. Moreover the availability of sensitive imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), have improved the detection of brain metastases (4, 13, 19-23). Brain lesions have developed in some patients with negative second examination following primary chemotherapy (5, 22, 24, 25).

Brain metastasis from ovarian cancer occurs mainly by direct haematogenous seeding through the Virchow-Robin perivascular spaces or by retrograde lymphatic spread following meningeal involvement (18). Advanced tumour stage and high histological grade are risk factors for this complication (6, 7, 13, 16, 18, 20, 22, 25-27). For instance, Kumar *et al.* (18) have reported that 94% and 65% of 18 patients with brain metastases had stage III-IV and grade 3 disease, respectively. In the experience of LeRoux *et al.* (25), the interval between ovarian cancer diagnosis and brain metastasis detection was five times shorter in patients with stage III-IV disease than in those with stage I-II disease. Cohen *et al.* (7) reported that this interval was 4.73 years for patients with grade 1-2 tumours compared to 1.5 years for those with grade 3 tumours ($p=0.03$). Although

Table I. *Pattern of recurrences preceding brain metastasis.*

Pts	Time* (months)	Site of recurrence	Treatment	Response
1	35	Para-aortic N, pelvis	CBDCA + Doxil	CR
	57	Mediastinum, Abdomen	Weekly TAX	PR
	63	Supraclavicular N	Topotecan, Gemcitabine	PR
2	13	Liver	Doxil	PR
3	48	Abdomen	CBDCA+TAX	CR
4	12	Pelvic/aortic N	CBDCA+TAX	PR
5	20	Liver + spleen	CBDCA + Surgery + Doxil	CR
6	15	Pelvis + abdomen	Surgery + Doxil	**
7	18	Abdomen+pleura	CBDCA + TAX	CR
8	12	Lung	Doxil	SD

*Time from ovarian cancer diagnosis to recurrence detection. **The patient underwent secondary surgical cytoreduction with peritoneal residual disease <0.5 cm, followed by chemotherapy with Doxil. After the first cycle, the patient developed brain metastasis. Pts, patients; N, lymph node; CBDCA, carboplatin; CR, complete response; TAX, paclitaxel; PR, partial response; SD, stable disease.

there is no clear correlation with histological type, most patients with brain lesions have serous or mixed ovarian cancer (5-7, 26, 27).

The aim of this retrospective study was the assessment of the pattern of brain recurrence in ovarian cancer patients who had undergone surgery followed by platinum-based chemotherapy.

Patients and Methods

One hundred and ninety-five patients with ovarian cancer who had undergone surgery followed by platinum-based chemotherapy at the Division of Gynecology and Obstetrics of the University of Pisa between November 1999 and March 2005, were assessed.

The hospital records of 12 (6.1%) patients who developed brain metastasis following the completion of primary treatment, were reviewed in detail.

The tumour stage and histological diagnosis of each case were determined according to International Federation of Gynecology and Obstetrics (FIGO) criteria and the histological typing system of the World Health Organization (WHO), respectively. The tumours were graded as well- (G_1), moderately (G_2), or poorly (G_3) differentiated.

The planned combination chemotherapy consisted of six cycles of paclitaxel 175 mg/m^2 (3-hour infusion) plus carboplatin area under curve (AUC) 5-6 in 11 patients and single-agent carboplatin AUC 5 in one. After the sixth cycle of chemotherapy, 10 patients with no evidence of disease at clinical, serological, ultrasonographic and radiological examinations were defined as being in clinical complete response, whereas two patients were found to be in clinical partial response. Four of the clinically complete responders underwent a second-look surgery, which showed a pathological complete response in 3 patients and a macroscopic persistent disease in one patient. All patients with clinically or surgically detectable persistent disease, as well as some pathologically complete responders, received further chemotherapy.

All the patients were periodically followed-up with physical and gynaecological examinations serum CA 125, and abdominal-pelvic ultrasound, and further investigations where performed when indicated. Routine follow-up procedures did not include central nervous system imaging techniques, but brain CT and/or MRI were performed whenever neurological symptoms developed.

The cumulative probability of survival from the time of initial surgery was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables.

Results

The median age of patients at the diagnosis of ovarian cancer was 59.5 years (range, 51-78 years). According to the FIGO classification, 9 patients had stage III disease and 3 stage IV disease. Histologically, 8 tumours were serous, 2 undifferentiated, one tumour was endometrioid and one was clear cell. The tumour grade was G_2 in 6 patients and G_3 in 6. Residual disease after initial surgery was ≤1 cm in 2 patients and >1 cm in 10. Ascites was present in 7 patients. One patient developed breast cancer 13 months after the diagnosis of ovarian cancer, and then underwent quadrantectomy and axillary lymphadenectomy, followed by chemotherapy consisting of cyclophosphamide, epidoxorubicin, and 5-fluorouracil.

The brain was the first site of recurrent disease in 4 (33%) cases. Conversely, brain metastases were preceded by chemo-sensitive recurrences in other sites in 8 (67%) patients (Table I). It is noteworthy that one patient (No. 1) had 3 recurrences before the detection of brain metastases.

The median time to brain recurrence was 33.5 months (range, 13.5-86.5 months) (Table II). Brain metastases were single in 6 (50%) cases, and extra-cranial disease was present in 7 cases (58%).

Brain involvement was symptomatic in 10 patients, and asymptomatic in 2. In one of these latter, a cerebral

Table II. *Characteristics of brain metastasis in the present series.*

Pts	*Time to brain mts (months)	Number	Site	Symptoms	Extra-cranial mts	Treatment
1	86.5	multiple	cerebral and cerebellar	extremity weakness	abdomen, mediastinum, supraclavicular node	WBI
2	16	multiple	cerebral and cerebellar	extremity weakness	liver	WBI
3	49	multiple	cerebral and cerebellar	seizure	abdomen	γ-knife +CHT
4	28	single	cerebellar	headache	abdomen	SR+CHT
5	55	single	cerebral	none**	abdomen	SR
6	19	single	cerebral	headache	abdomen	Symptomatic
7	34	multiple	cerebral	headache and vomiting	no	WBI
8	13.5	multiple	cerebral	impaired deambulation	Abdomen + mediastinum	WBI+CHT
9	20	single	cerebral	none**	no	Surgery
10	38	single	cerebral	impaired deambulation	no	SR
11	21.5	multiple	cerebral	impaired deambulation	no	Symptomatic
12	21	single	cerebral	extremity weakness and headache	no	Surgery + WBI

*Time from ovarian cancer diagnosis to brain metastasis detection. **Brain metastasis detected after CT scan, see main text. Pts, patients; mts, metastasis; WBI, whole brain irradiation; CHT, chemotherapy; SR, stereotactic radiosurgery.

metastasis was detected during a brain CT scan required for patient inclusion in an experimental trial with an anti-angiogenetic agent for abdominal relapse. In the other patient, a single cerebral lesion was found at a brain CT scan performed as a staging examination for local recurrence of breast cancer. The patient underwent surgical resection of the brain lesion that was shown to be a metastasis from the serous ovarian cancer.

Of the other 5 women with single brain metastasis, one patient underwent surgical resection followed by whole brain irradiation, 3 patients received stereotactic radiotherapy (followed by paclitaxel-/platinum-based chemotherapy for coexistent extra-cranial recurrence in one case), and one patient had only symptomatic treatment.

Of the 6 patients with multiple brain metastases, 4 received whole brain irradiation (followed by chemotherapy with doxil for concurrent extra-cranial recurrence in one case), one patient had gamma–knife irradiation of three cerebral lesions (followed by paclitaxel-/platinum-based chemotherapy for concurrent extra-cranial recurrence), and one patient had only symptomatic treatment.

Whole brain irradiation consisted of 30 Gy in 10 fractions over 2 weeks in all the cases.

The median survival from diagnosis of brain metastasis was 8.3 months (range, 1-28 months) (Figure 1). Survival was not related to the number of brain metastases (multiple *versus* single) (data not shown), presence or absence of extra-cranial disease (data not shown), or interval between ovarian cancer diagnosis and brain metastasis detection ($<$33.5 months *versus* $\geq$33.5 months) (data not shown).

Discussion

Brain metastases represent a relatively uncommon event in ovarian cancer, which occurs more often in patients with prolonged survival (6). A slight increase in their incidence has been observed in the recent years. For instance, in the series at the Royal Marsden Hospital, central nervous system metastases occurred in 0.2% of the 945 patients treated from 1980 and 1984, 0% of the 933 patients from 1985 and 1989, 0.3% of the 958 patients from 1990 and 1994, and 1.3% of the 854 patients from 1995 to 1999 ($p<0.001$).

Data from the literature showed that the median age at presentation ranged from 52 to 58 years, approximately, the median interval between ovarian cancer diagnosis and brain metastasis detection ranged from 14.5 to 46 months, brain metastases were multiple in 25% to 75% of cases and were associated with extra-cranial disease in 23% to 100% of cases (5-7, 15, 16, 18, 19, 21, 25, 27, 28) (Table III). The clinical manifestations of cerebral metastases depend on the site of the disease, with headache being the most common symptom (40-50% of the cases) mainly due to increased intra-cranial pressure (5-7, 12, 18, 20, 26, 27). Other frequent symptoms and signs included extremity weakness, hemi-paresis, tremors, confusion, seizures, vertigo, vomiting, speech disturbance, and visual disturbance (5-8, 16, 18, 25, 26). The characteristics of brain metastases in ovarian cancer in our study are in agreement with the literature.

Survival after the diagnosis of brain metastasis is generally poor (5, 6, 10, 17, 25, 26, 28). In the series of Geisler and Geisler (5) median survival was 18.5 months (range, 1-24

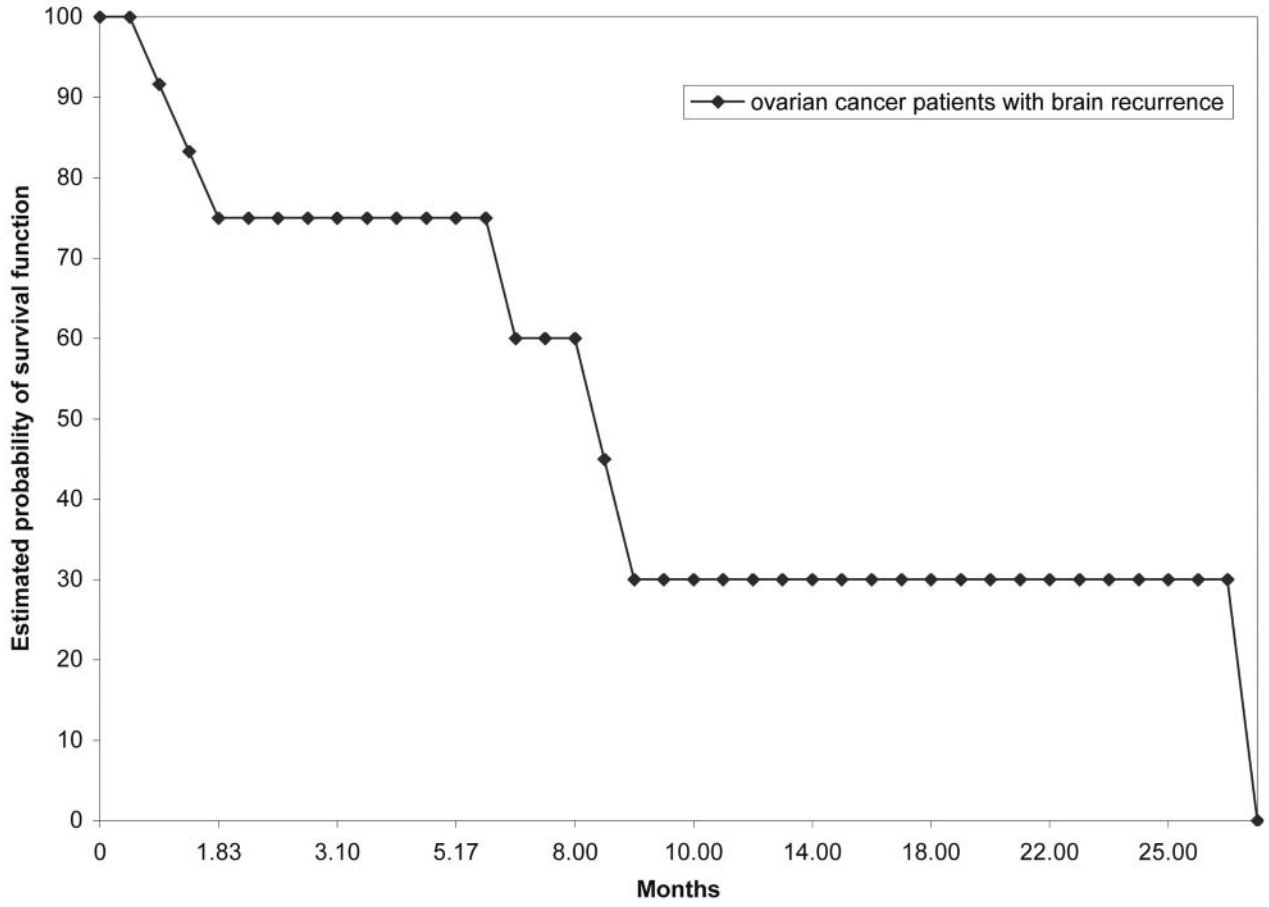

Figure 1. *Survival after diagnosis of brain recurrence.*

months) for patients with a single metastasis compared to 2.5 months (range, 1-17 months) for those with multiple lesions ($p=0.058$). In the study of Chen *et al.* (28) the presence of multiple metastases was an independent poor prognostic factor for survival ($p=0.03$). Collected data from 124 patients revealed that the only variable affecting survival was the presence or absence of additional distant lesions, with a median survival of 3 and 8 months, respectively ($p=0.005$) (17). In the series of Cormio *et al.* (27), including 22 patients who underwent surgical resection of a single brain metastasis, the median survival was 21 months for the patients with brain metastases as a unique site of disease compared to 9 months ($p=0.04$) for those with other tumour sites. In the same study, the median survival was 22 months for patients with an interval between ovarian cancer diagnosis and brain metastasis detection greater than 29 months *versus* 7 months for those with a shorter time interval ($p=0.02$).

In the present series, the median survival from diagnosis of brain metastasis was 8.3 months. The clinical outcome of patients was not related to the number of brain metastases, the presence or absence of extra-cranial metastases, or the interval between ovarian cancer diagnosis and brain metastasis detection, probably because of the limited number of cases.

The therapeutic approach is different for isolated, single metastases compared to multiple metastases. Patients with isolated, single brain metastases generally undergo neuro-surgical resection followed by whole brain irradiation, and this treatment modality appears to achieve a longer survival when compared to either surgery or irradiation alone (7, 16, 18, 19, 21, 25-27, 29, 30). For instance in the series of Cohen *et al.* (7) median survival was 23.1 months for patients who received this integrated treatment *versus* 5.3 months for those who underwent whole brain irradiation alone ($p<0.01$) and *versus* 6.9 months for those who underwent surgery alone ($p<0.01$). D' Andrea *et al.* (30) reported a mean survival of 28 months among 11 patients with single brain metastases treated by surgical en bloc removal followed by radiotherapy and chemotherapy, and the cause of death was a systemic relapse in all cases. However, approximately 50% of the patients with solitary brain metastases are not

Table III. *Characteristics of brain metastasis: collected data from the literature.*

Author (ref.)	Pts n	Age at brain mts	Time* (months)	Multiple mts n (%)	Extra-cranial disease N (%)	Survival from brain mts (months)
Geisler and Geisler (5)	16	_	19.0	8 (50)	8 (50)	3.0
Kolomaimen *et al.* (6)	18	57.0	46.0	9 (50)	10 (55.5)	7.0
Cohen *et al.* (7)	72	53.7	22.0	47 (65)	41(57)	6.3
Tay *et al.* (8)	4	-	16.5	3 (75)	4(100)	19.5
Rodriguez *et al.* (12)	15	57.0	18.5	10 (67)	4 (40)	9.0
Corn *et al.* (15)	32	56.0	24.0	17 (30)	20 (62.5)	4.0
Kaminsky-Forrett *et al.* (16)	8	58.0	15.0	2 (25)	7 (87)	3.0
Anupol *et al.* (17)	15	-	22.0	7 (47)**	7(47)	6.0
Kumar *et al.* (18)	18	54.0	29.0	12 (67)	13 (72)	7.2
Pectasides *et al.* (19)	17	58.0	15.9	13 (65)	4 (23)	5.7
McMeekin *et al.* (21)	15	-	19.5	6 (41)	-	6.0
LeRoux *et al.* (25)	14	52.5	14.5	5 (36)	8 (57)	3.0
Cormio *et al.* (27)	22	56.0	29.0	0	13 (59)	16.0
Chen *et al.* (28)	19	54.0	25.2	12 (63)	10 (83)	16.0

*Time from ovarian cancer diagnosis to brain metastasis detection. **One patient had MRI negative for brain lesion, but spinal fluid was positive for metastatic cells consistent with primary ovarian cancer. ref., Reference; Pts, patients; mts, metastasis.

candidates for surgery because of extracranial disease or tumour inaccessibility. Stereotactic radiosurgery allows the delivery of high doses of focused radiation by either a linear accelerator or a gamma-knife to a small intra-cranial target while sparing the surrounding normal brain (31, 32). No randomised prospective trials comparing surgery *versus* stereotactic radiosurgery for the treatment of single brain metastases have been conducted, and two retrospective studies showed contradictory results (33, 34). Stereotactic radiosurgery appears to be especially useful for patients with a single lesion who are unable to tolerate surgery and for those with surgically inaccessible lesions (35).

Whole brain irradiation with or without chemotherapy is the treatment of choice for multiple brain metastases, with or without extracranial disease, but achieves a median survival of 3 to 10 months only (7, 12, 15-18, 20, 26, 36-38). In a randomised phase III study of the Radiation Therapy Oncology Group (RTOG), accelerated hyper-fractionated radiotherapy (1.6 Gy b.i.d.) to a total dose of 54.4 Gy failed to improve survival compared with a conventional regimen of 30 Gy in 10 fractions (39).

The significance of chemotherapy in managing brain metastases is still controversial. Some studies with systemic chemotherapy have shown objective responses and promising survival rates for patients with cerebral metastases from breast cancer and germ cell tumors, and recently, even from ovarian cancer (10-12, 14, 27, 40-44). Cooper *et al.* (14) reported one complete response and 2 partial responses among 3 ovarian cancer patients with brain metastases treated with the single agent carboplatin. A patient with multiple brain metastases achieved a complete response following whole brain irradiation and sequential chemotherapy consisting of cisplatin and gemcitabine (10). Three subsequent brain relapses were controlled by a combination chemotherapy including 5-fluorouracil, cisplatin and gemcitabine. The combination of carboplatin plus docetaxel obtained a complete response in a patient who developed multiple brain and meningeal metastases ten months after completion of primary treatment with the same chemotherapy regimen (44). However meningeal disease recurred four months later, and rapidly led to the patient's death. The progressive growth of brain metastases may compromise the integrity of the blood- brain barrier, thus explaining the possible response of brain metastases to systemic chemotherapy (20, 27, 41, 43). However, the role of this treatment modality for brain metastases from ovarian cancer deserves further clinical investigation.

In conclusion, the incidence of brain metastases in ovarian cancer patients is still low, but as more effective systemic therapies are available, their incidence is likely to increase. Patients with single brain metastases usually undergo surgery followed by whole brain irradiation or stereotactic radio-surgery if unsuitable for surgical resection. Patients with multiple brain lesions with or without systemic disease have a very poor prognosis but can draw some benefit from whole brain irradiation with or without systemic chemotherapy. Only palliative, supportive cures, with corticoids, mannitol, and anticonvulsant agents, can be used in patients with poor performance status, advanced age, or progressive widespread systemic disease (20).

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Received June 4, 2007
Revised September 4, 2007
Accepted September 28, 2007