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Brain Metastases from Epithelial Ovarian Cancer. The Hellenic Cooperative Oncology Group (HeCOG) Experience and Review of the Literature

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Abstract. *Background: Brain metastases from epithelial ovarian cancer (EOC) are rare. A retrospective study of all patients diagnosed with brain metastases from EOC over the last 20 years, according to the Hellenic Cooperative Oncology Group (HeCOG) tumor registry, was conducted. Patients and Methods: A total of 1450 patients with EOC were treated within various HeCOG protocols from 1983 to 2004. Seventeen (1.17%) of them developed brain metastases. Results: The median age at diagnosis of brain metastases was 58 years (range, 24 to 77). At initial diagnosis, 2 patients had stage II, 12 had stage III and 3 had stage IV disease. Serous papillary adenocarcinoma was the most common histological subtype [12 patients (71%)]. All patients had received initial cisplatin-based chemotherapy. The median time from initial diagnosis to central nervous system (CNS) relapse was 15.9 months (range, 1.4 to 70.8). The CNS was the only site of disease in 13 (76.5%) patients, whereas 4 (23.5%) patients had additional extracranial disease. Two (12%) patients with isolated single brain lesions underwent surgical excision of the metastases, followed by whole brain radiation therapy (WBRT) and chemotherapy. Four (24%) patients were treated with WBRT alone, 6 (35%) patients with WBRT plus chemotherapy and 2 (12%) had only supportive care, while 3 (18%) patients decided not to have any further treatment after the diagnosis of brain metastases. The median survival time from diagnosis of CNS relapse was 5.7 months (range, 0.2 to 22.6) and the median survival time from diagnosis of EOC was 27.4 months (range, 3.0 to 71.4). In patients with CNS recurrence as the only site of disease, the median survival time from diagnosis of CNS relapse was 5.3 months (range, 0.6 to 22.6) and in those with both CNS and extracranial disease, the median survival time was 3.9 months (range, 0.2 to 11.9) (p=0.5597). There was a statistically significant difference in survival for those treated with WBRT plus chemotherapy (10.0 months) versus those treated with WBRT alone (1.5 months) and those who had only supportive care (0.2 months) (p=0.0003). Conclusion: The incidence of cerebral metastases in our patients with EOC was 1.17%, which is consistent with the mean value of all series reported in the literature. The prognosis of patients with brain metastases from EOC is poor. Patients who had WBRT and chemotherapy fared better than those who received WBRT alone.*

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Brain metastases from epithelial ovarian cancer (EOC) constitute a rare and late manifestation of the disease and occur in patients with prolonged survival following platinum-based chemotherapy. Mayer *et al.* reported 5 cases in 567 autopsies performed on patients with EOC, accounting for an incidence of 0.9% (1). Several authors have recently called attention to the rising incidence of brain metastases in EOC (2, 3). In a series of 42, 110 and 52 EOC patients, the incidence of brain metastases was reported as 7.1%, 4.5% and

11.6%, respectively, but these studies concerned rather small numbers of patients (3-5). Some reports indicated that the rate was greater than 5% and was approaching 12 % (5, 6).

Traditionally, brain metastases have been managed with whole brain irradiation (7-9). Although this approach is generally effective for short-term palliation, the reported median survival in patients treated in this manner was 4 months (9), and the failure rates ranged between 11% and 50% (10). Therefore, certain subsets of patients (*e.g.* small lesion, good performance status, lack of systemic disease burden) may be candidates for surgical resection or stereotactic irradiation (11, 12). A recent report suggested that carboplatin is an effective treatment for EOC metastatic to the brain (13). Multimodal treatment, including surgery, radiation and chemotherapy, leads to an increased median survival (14, 15).

We here present the experience of the Hellenic Cooperative Oncology Group (HeCOG) on brain metastases from EOC over the last 20 years.

Patients and Methods

All patients with brain metastases from EOC, registered in the HeCOG's electronic tumor registry between July 1983 and July 2004, were considered for analysis. In all cases, the diagnosis of brain metastases was confirmed by review of the corresponding clinical notes. Patients were included in the study only if their diagnosis had been confirmed on CT scan or MRI of the brain. Patients with a past history of malignancy other than EOC or evidence of a synchronous primary tumor were excluded from the study. Patients with non-epithelial ovarian cancer or those with carcinosarcoma of the ovaries were also excluded.

All patients had initially undergone a surgical staging, with an intention to optimal cytoreduction including bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy and aggressive cytoreductive surgery for those with advanced-stage disease. Patient demographics, clinical variables, treatment and survival data were extracted from the patients' charts and from the electronic HeCOG tumor registry. Variables included age at diagnosis, date of diagnosis, FIGO stage, tumor grade, ECOG performance status at diagnosis, measurability of disease, residual disease following primary surgery (classified as 0, ≥2, or <2 cm), serum CA-125, chemotherapy regimen, response to chemotherapy, site of recurrence, treatment for recurrence, time to relapse, time to relapse in the brain and survival from the diagnosis of brain metastases and the overall survival from the diagnosis of primary tumor to the last follow-up or until the patient's death.

On diagnosis of brain metastases, patients were managed by surgical excision and/or radiotherapy, with or without concomitant chemotherapy, or only palliative treatment. Irradiated patients received a total dose ranging from 30 Gy (3 Gy per fraction in 10 fractions) to 45 Gy (1.8 Gy per fraction in 25 fractions). Some patients received a boost dose of 10 Gy to the bed of the tumor. All patients received dexamethasone simultaneously.

Subjective patient impressions and objective measurements by clinicians and radiologists were used to determine response, including age, stage, histological differentiation, residual disease following primary surgery, the number of chemotherapy regimens or cycles, the ECOG performance status, the number of brain metastases (solitary *versus* multiple), the status of extracerebral metastases (present, absent) and the use of concomitant systemic therapy.

The Kaplan-Meier method (16) was used to calculate survival, while the log rank test was used to compare time to event distributions.

Table I. *Patient and tumor characteristics.*

N	17
Age (years)	
Median	58
Range	24 - 77
ECOG Performance Status	
0	7 (41%)
1	7 (41%)
2	1 (6%)
Unknown	2 (12%)
Histology	
Serous	12 (71%)
Mucinous	2 (12%)
Endometrioid	2 (12%)
Adenocarcinoma	1 (6%)
Grade	
II	3 (18%)
III	11 (65%)
Unknown	3 (18%)
Stage	
II	2 (12%)
III	12 71(%)
IV	3 (18%)
Residual disease (cm)	
0	2 (12%)
< 2	3 (18%)
2-5	2 (12%)
> 5	7 (41%)
Unknown	3 (18%)
Initial surgery	
TAH + BSO ± omentectomy ± appenticectomy	13 (76%)
Other (biopsies, USO, BSO, omentectomy)	4 (24%)

TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, USO: unilateral salpingo-oophorectomy

Results

From July 1983 to July 2004, 1450 women were registered in the HeCOG's electronic database as having histologically confirmed EOC; 17 (1.17%) of them developed brain metastases.

The characteristics of these 17 patients are listed in Table I. The median age at the time of diagnosis of EOC was 56 years (range 24 to 75 years), and the median age at the time of central nervous system (CNS) relapse was 58 years (range 24 to 77 years). An analysis of the initial FIGO staging classification revealed 2 patients with stage II, 11 patients

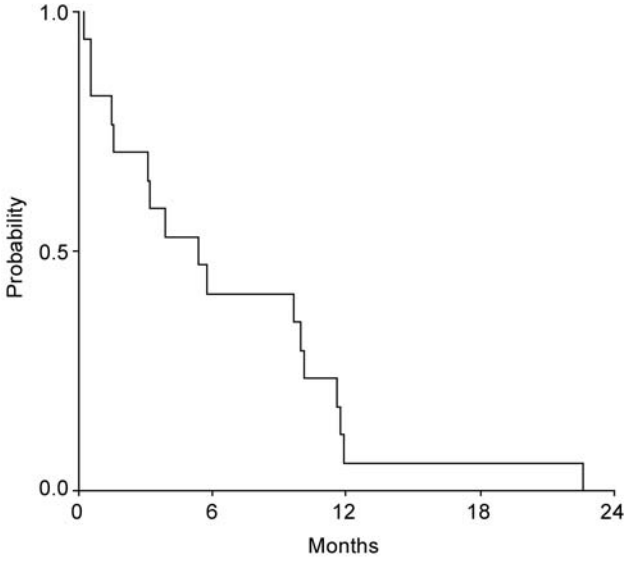

Figure 1. *Survival in patients with epithelial ovarian cancer from the diagnosis of central nervous system relapse.*

Table II. *Incidence of CNS metastases in patients with primary EOC.*

Author (year)	Study period	No. of patients with EOC	No. of patients with CNS metastases	Incidence (%)
Mayer (1978)	1973-1979	576	6	1.04
Baker (1981)	1969-1979	430	4	0.93
Piura (1990)	1961-1988	200	2	1.0
Rodriguez (1992)	1977-1990	795	15	1.89
Bruzzone (1993)	1981-1989	413	9	2.18
Cooper (1994)	1987-1992	230	3	1.30
Corn (1995)	1965-1994	4027	32	0.79
Kaminsky-Forrett (2000)	1974-1998	704	7	0.99
Anuprol (2002)	1986-2000	1042	15	1.44
Kolomainen (2002)	1980-1999	3690	18	0.49
Kumar (2003)	1991-2001	795	18	2.26
Present study (2005)	1983-2004	1450	17	1.17
Total		14352	146	1.02

EOC: epithelial ovarian cancer, CNS: central nervous system.

with stage III and 3 patients with stage IV disease. Serous papillary adenocarcinoma was the most common histological subtype (12 patients), followed by mucinous (2 patients) and endometrioid (2 patients). One patient was reported as having an adenocarcinoma. Three patients had grade II tumors and 11 patients had grade III tumors. Grading was not reported in 3 patients. Of the 17 patients, 7 had optimal primary cytoreduction with residual disease <2 cm, 2 of whom had no residual tumor. All patients had received initial platinum-based chemotherapy.

Brain CT scan was performed in all patients. The diagnosis of CNS metastases was based on abnormalities in either CT scans or MRI of the brain or both in all patients. The diagnosis was confirmed by surgical excision in 2 patients; the histology of the resected brain metastases was consistent with their original primaries. All patients with brain metastases were also evaluated for the presence of any extracranial systemic disease.

The presenting symptoms of CNS recurrence varied according to the area involved. The clinical presentation of patients included features of increased intracranial pressure (headache, nausea/vomiting, papiledema), extremity weakness, seizures, vertigo, vision problems, tremors, aphasia and altered consciousness. Five patients had single lesions, while 12 patients presented with multiple metastases.. The CNS was the only site of disease in 13 patients, whereas 4 patients had additional extracranial disease (1 patient had pelvic disease, 1 patient had pelvic disease and ascites, 1 patient had pelvic disease, ascites and supraclavicular node metastases and 1 patient had parenchymal lung disease and pleural effusion). Two patients with isolated single brain metastases underwent surgical excision of the metastases. Surgery was followed by whole brain radiation therapy (WBRT) and chemotherapy. Four patients received WBRT alone (30 Gy in 10 fractions or 45 Gy in 25 fractions), 6 patients received WBRT plus chemotherapy, 2 patients had only supportive care due to poor general status and disseminated disease and 3 patients decided not to have any further treatment after the diagnosis of brain metastases. All patients received at least one line of cisplatin-based chemotherapy. Out of 17 patients, 9 received only one line of chemotherapy, 2 received two lines of chemotherapy, 4 received three lines of chemotherapy and 2 received four lines of chemotherapy.

The median interval from diagnosis of EOC and documentation of brain metastases was 15.9 months (range, 1.4 to 70.8 months). The median survival from diagnosis of CNS relapse was 5.7 months (range, 0.2 to 22.6 months, Figure 1) and the median survival from diagnosis of EOC was 27.4 months (range, 3.0 to 71.4 months). In patients with CNS recurrence as the only site of disease, the median survival time from the diagnosis of CNS relapse was 5.3 months (95% CI 2.2 to 8.5, range, 0.6 to 22.6 months). In patients with both CNS and extracranial disease, the median survival time was 3.9 months (95% CI 0.0 to 15.1, range 0.2 to 11.9 months). This difference was not statistically significant ($p=0.5597$). All patients died from the disease.

Patients with unifocal CNS recurrence had a median survival after diagnosis of 5.3 months, with a range from 0.5 to 22.6 months (95% CI, 0.0-10.2), and those with multifocal recurrences had a median survival of 3.9 months and a

Table III. *Stage, histology, grade and number of metastases.*

	No. of patients			
	Literature	Present study	Total	%
FIGO stage				
I	21	0	21	9.33
II	24	2	26	11.56
III	123	12	135	60.00
IV	40	3	43	19.11
Total	**208**	**17**	**225**	**100.00**
Histology				
Serous	77	12	89	68.46
Mucinous	4	2	6	4.62
Endometrioid	14	2	16	12.30
Clear cell	1	0	1	0.77
Undifferentiated	6	0	6	4.62
Adenocarcinoma	11	1	12	9.23
Total	**113**	**17**	**130**	**100.00**
Grade				
I	6	0	6	3.45
II	55	3	58	33.33
III	99	11	110	63.22
Total	**160**	**14**	**174**	**100.00**
No. of CNS metastases				
Single	87	5	92	41.63
Multiple	104	12	116	52.49
Meningeal	13	0	13	5.88
Total	**204**	**17**	**221**	**100.00**

range from 0.2 to 11.9 months (95% CI, 0.0-8.2). The difference in survival among patients with single *versus* multiple CNS recurrence was not statistically significant ($p=0.6538$). Patients with non-serous histology (5.7 months) had a slightly better survival than those with a serous histology (3.9 months) ($p=0.4583$), but this difference was not statistically significant. Those with grade II tumors survived longer than those with grade III tumors (10.0 months, *versus* 5.3 months, $p=0.9653$). There was a statistically significant difference in survival for those treated with WBRT and chemotherapy *versus* those treated with WBRT alone and those who had only supportive care ($p=0.0003$). The median survival time from the diagnosis of brain metastases was 10.0 months, 1.5 months and 0.2 months for these three groups of patients, respectively However, survival for those undergoing craniotomy plus WBRT *versus* those treated with WBRT plus chemotherapy, without craniotomy, did not differ significantly ($p=0.3963$).

Discussion

CNS involvement in EOC is a rare complication with the mean reported incidence being 1.01% (15). Recent studies showed that the incidence of brain metastases has increased over time to 2-4% (Table II) (17). Possible reasons for this increase observed during the past three decades include changes in the natural course of EOC, due to improved primary control of intra-abdominal disease with platinum-based chemotherapy, resulting in longer survival and allowing metastases in distant sites to implant and grow, as well as to the availability of better imaging techniques for diagnosis of brain metastases (6, 17-20). In addition, chemotherapy may cross the blood-brain barrier poorly, thus increasing the propensity of CNS metastases. Metastases to the CNS from EOC have been postulated to occur *via* direct hematogenous seeding through Virchow-Robin perivascular spaces, retrograde lymphatic spread from meningeal involvement or direct invasion into CNS after bony involvement (15).

The median age of our patients was 56 years, which is consistent with that reported by other investigators (4, 15, 21). The survival, based on age of patients who subsequently developed brain metastases, showed no statistical significance between patients aged <55 and ≥ 55 years ($p=0.1884$). Most of our patients (88%) with brain metastases had stage III and IV disease at the time of initial diagnosis. A review of the literature revealed that the frequency of patients with stage III or IV disease and brain metastases is greater than 75% (15). However, in the series of Kolomainen *et al.* (22), an unusual proportion (1/3) of the patients with CNS involvement had stage I disease The most common histological grade in our patients was III, which is consistent with the experience of other investigators (Table III) (15, 18, 23). In addition, this is in accordance with the belief that advanced disease and poorly-differentiated tumors at the time of initial diagnosis place a patient at an increased risk for CNS metastases (19). In contrast, other investigators reported that the degree of histological differentiation does not seem to be clearly correlated with brain metastases (23, 24). There was no statistically significant improvement in survival with lower-grade lesions in our patients and in those of others (25). Most of the cases, both in the literature and in our series, had a tumor of the serous subtype, the most common histological variation in EOC (15, 18, 23, 26).

The most common presenting symptoms were those related to increased intracranial pressure, such as headache, nausea/vomiting and papiledema. Less common symptoms included extremity weakness, seizures, speech impairment, vision problems, dysphasia, confusion and altered consciousness.

Most of our patients with CNS involvement had no active intra-peritoneal disease, which is not consistent with the experience of others (3, 18, 23). In our series, 13 patients (76.5%) had an isolated CNS relapse and 4 (23.5%) had both CNS and extracranial disease. Sanderson *et al.* (27)

reported a higher proportion of patients as having extra-peritoneal disease at the time of diagnosis, while Kolomainen *et al.* (22) showed that approximately 50% of patients had CNS as the only site of recurrent disease. In addition, some of the relapsing patients were complete responders after first-line chemotherapy. The presence of distant metastases aside from the brain disease seems to have an adverse effect on survival. Due to the relative lack of effective salvage chemotherapy, most patients shared a similar course of progressive intra-abdominal disease irrespective of the intracranial disease state. The cause of death in the majority of patients was related both to the brain metastases and to the abdominal spread of disease.

Routine CT scan of the brain is not usually recommended when following EOC patients, because follow-up procedures focus on the documentation of intra-abdominal relapse and do not usually include an evaluation of the CNS with imagine techniques. However, in the case of neurological symptoms, diagnosis of CNS metastases becomes obvious on CT scan or MRI in most cases.

In our series, multiple brain metastases were observed in 12 out of 17 patients. In the reviewed series, the brain metastases were single in 43% of patients, multiple in 50.1%, while 6.3% of patients had meningeal involvement (Table III).

Because of the rarity of these patients, the optimal treatment for brain metastases in EOC is currently ill-defined. The therapeutic approach of EOC with brain metastases must take into account the number and the location of metastases, the presence or absence of extracranial disease, previous treatment, performance status and neurosurgery possibilities. Therapy of brain involvement included surgery, radiation therapy, chemotherapy and palliative care. Traditionally, for patients with isolated CNS relapse, with single and/or resectable metastases, surgical resection followed by WBRT and systemic chemotherapy is a realistic option. In our review of the literature, only 57/227 patients underwent surgery for brain metastases in all the series (15, 28, 29). Radiotherapy was administered after brain surgery. For patients with multiple brain metastases, WBRT, with or without chemotherapy, remains the treatment of choice. Palliative radiotherapy alone was administered in 50% of patients with multiple brain metastases of all the series. Radiotherapy, or radiotherapy in combination with surgical resection and/or chemotherapy, were the most commonly used therapies, representing 40.4% and 35.6% of the cases reviewed, respectively. Chemotherapy is frequently administered in the presence of other sites of recurrence. It may be possible to use cisplatin, particularly in patients who had previously documented response to platinum-based chemotherapy or for chemotherapy-naive patients. Complete response of brain metastases after carboplatin has been reported in the literature (13, 30-32). In the reviewed series 12.3% (28/227) of the patients received no treatment or steroids to manage the brain metastases.

In conclusion, CNS metastases in EOC are a rare and probably late manifestation of the disease. In patients with isolated solitary CNS metastases, craniotomy and metastasectomy followed by WBRT may be beneficial. Patients with multiple CNS metastases, with or without systemic disease, have a poor prognosis and have a small benefit from WBRT and/or systemic chemotherapy. The role of chemotherapy in the treatment of brain metastases is unclear.

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