

Epithelial Ovarian Cancer Metastasizing to the Brain: A Late Manifestation of the Disease With an Increasing Incidence

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Purpose: We present the Royal Marsden Hospital experience of cerebral metastases from primary epithelial ovarian carcinoma (EOC) over the last 20 years and examine the evidence for an increasing incidence of EOC metastasizing to this site.

Patients and Methods: A total of 3,690 women with EOC were seen at the Royal Marsden Hospital from 1980 to 2000. Eighteen of these patients developed cerebral metastases.

Results: Median age at diagnosis of EOC was 52 years (range, 39 to 67). All patients received at least one line of platinum-based chemotherapy; 56% (10 of 18) received more than one line of treatment; 17% (three of 18), two lines; 11% (two of 18), three lines; and 28% (five of 18), four lines. The median treatment interval between each line of chemotherapy was 12, 18, and 4 months. The median interval between diag-

nosis and CNS relapse was 46 months (range, 12 to 113), in comparison with 5 and 7.5 months for hematogenous relapse in lung or liver, respectively ($P < .001$). The incidence of CNS metastases in our population from 1980 to 1984 was 0.2%; from 1985 to 1989, 0%; from 1990 to 1994, 0.3%; and from 1995 to 1999, 1.3% ($P < .001$). An analysis of data from the literature also suggests that the incidence of cerebral metastases from EOC has increased over time.

Conclusion: CNS metastases in EOC are a rare and late manifestation of the disease, occurring in patients with a prolonged survival caused by repeated chemosensitive relapses. An analysis of our data and the data from the literature suggests that the incidence of metastasis at this site in patients with EOC is increasing.

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EPITHELIAL OVARIAN carcinoma (EOC) is the fifth most common cancer in women in the industrialized nations; more than 26,000 women are diagnosed annually in the United States.¹ The majority of women present with advanced (stage III to IV) disease, and despite debulking surgery and platinum-based chemotherapy, only 20% to 30% of women will be alive at 5 years.² EOC is a disease that remains locoregionally confined until late in its natural history, and hematogenous metastases are rare at presentation (16%), with the most common sites of metastatic spread being the pleural cavity (33%), liver (26%), and lung (3%).³

CNS metastasis from EOC is rare. Mayer et al,⁴ in a postmortem study, identified five such patients out of 567 (0.9%) women with EOC. Subsequently a number of other case series have reported an incidence of clinically apparent cerebral metastases in EOC patients of 0.9% to

3.3% in patient populations numbering from 430 to 795.⁵⁻⁸ Some of these reports have suggested that there has been an increase in the incidence of cerebral metastasis from EOC, but this assertion has never been supported by a longitudinal analysis of the data. We present here the Royal Marsden Hospital experience of cerebral metastases from primary EOC over the last 20 years and examine the evidence for an increasing incidence of metastases at this site.

PATIENTS AND METHODS

Patients

All patients presenting to Gynaecological Cancer Unit, The Royal Marsden Hospital, London, United Kingdom, had their clinical characteristics, surgical details, and pathologic diagnosis entered into a prospective computerized database. The database records patients' stage at surgery according to the International Federation of Gynecology and Obstetrics classification; the sites of disease; the dates and dosage of any therapy, such as chemotherapy or radiotherapy, given; tumor responses as assessed clinically or radiologically according to World Health Organization criteria; and follow-up information, such as the dates of relapses and death. Surgical interventions are also documented, as are details of any history of cancer or a family history of malignancy. Treatments given to the patients before referral are also entered into the database.

Patient Identification

The database of patients with EOC was searched for those who were recorded as having cerebral metastases from January 1980 to June

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2000. Patients who had a history of malignancy other than EOC or evidence of a synchronous primary tumor were excluded from this analysis, except patients with in situ carcinoma of the cervix and nonmelanoma skin cancer. Patients with non-EOC or with carcinosarcoma were excluded from the study. The patients identified from the database as having cerebral metastases had their diagnosis confirmed by review of their clinical notes, with particular attention to the results of histologic review and radiology. Patients were included in the study only if their diagnosis had been confirmed on computed tomography (CT). The CT scans of patients with brain metastases who presented to other institutions were reviewed at the Royal Marsden Hospital on referral.

Data Collected

The following patient characteristics were extracted from the research database and cross-checked with the patient clinical notes: age, stage, completeness of initial surgery, residual disease after this surgery (classified as none, < 2 cm, or > 2 cm), histology, tumor grade, type of chemotherapy instituted, response to chemotherapy, site of recurrence, therapy for recurrence, time to relapse, and survival. Patients who underwent laparotomy, total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and partial or total omentectomy were classified as having had complete surgery. Histologic material was reviewed at the time of diagnosis of ovarian cancer and was classified as serous, mucinous, endometrioid, or other, which included fallopian tube carcinoma and mixed epithelial histology. Differentiation was recorded as well differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3) or was not recorded. The diagnosis of recurrence at other sites was made on clinical assessment, radiologic assessment, or both.

RESULTS

Patient Characteristics

From January 1980 to June 2000, 3,690 women were registered in the Royal Marsden Hospital Gynaecology Unit database as having histologically confirmed EOC; 18 (0.49%) of these women developed CNS metastases (Table 1). The median age of our patients with cerebral metastasis at diagnosis of their ovarian cancer was 52 years (range, 39 to 67 years). The median age at the time of CNS relapse was 57 years (range, 43 to 71 years). Clinical staging at initial diagnosis was as follows: stage I, six (33%) of 18; stage II, three (17%) of 18; stage III, seven (39%) of 18; and stage IV, two (11%) of 18. Six patients (33%) had complete surgery, ie, TAH, BSO, and omentectomy. Twelve patients (67%) underwent TAH and BSO only (six stage I, two stage II, three stage III, and one stage IV). Suboptimal cytoreductive surgery was performed in six patients (33%) with advanced disease. The histologic subtype of the tumors was as follows: 72% (13 of 18) serous, 5.5% (one of 18) mucinous, 5.5% (one of 18) endometrioid, and 17% (three of 18) other types. No patient had a well-differentiated tumor; all tumors were of either moderately (44%) or poorly differentiated (56%) histologic grade. Two patients had histologic confirmation that their cerebral

Table 1. Patient Characteristics

Characteristic	No. of Patients/Total	%
Stage at presentation		
I	6/18	33
II-IV	12/18	67
Histologic type		
Serous	12/18	67
Mucinous	1/18	5.5
Endometrioid	1/18	5.5
Other	4/18	22
Histologic grade		
1		
2	8/18	44
3	9/18	50
Not recorded	1/18	6
Residual disease at presentation		
None	5/18	28
< 2 cm	4/18	22
> 2 cm	7/18	39
Not recorded	2/18	11
Type of initial surgery		
Optimal cytoreduction	6/18	33
Suboptimal cytoreduction	12/18	67
No. of lines of chemotherapy		
1	8/18	44
2	3/18	17
3	2/18	11
4	5/18	28
Response rate		
First line	13/18	72*
Second line	8/10	80
Third line	3/7	43
Fourth line	2/5	40

*Three patients were not assessable.

metastases were of ovarian origin: one at surgery and the other at postmortem.

Presentation of CNS Relapse

Presenting symptoms of CNS recurrence varied according to the site of disease (not recorded in one patient). The most common symptoms associated with CNS metastases were motor weakness (six patients), confusion (six patients), headaches (five patients), and seizures (three patients). Symptoms of aggression, vomiting, speech disturbance, and visual disturbance also occurred. All CNS recurrences were diagnosed by CT scan (Fig 1). Nine patients had a solitary deposit, and the rest had multiple metastases. The CNS was the only site of disease in eight patients, whereas the other 10 patients had additional sites of involvement. All 10 had parenchymal lung or liver metastases, nine patients also had peritoneal disease in the abdomen or pelvis, and six patients had intra-abdominal lymphadenopathy.



Fig 1. Axial contrast-enhanced CT scan of the brain demonstrates multiple metastases.

Timing of CNS Relapse

The median time from diagnosis of ovarian cancer to the first site of relapse was 25.5 months (range, 10 to 58 months), and the median time from diagnosis to documentation of CNS metastasis was 46 months (range, 12 to 113 months; Table 2). The median time to relapse for patients in the gynecology database with liver ($n = 416$) or lung ($n = 811$) metastases was 5 and 7.5 months, respectively ($P < .001$ v median time to CNS relapse; Fig 2). The median interval from the chemotherapy treatment immediately preceding a diagnosis of CNS relapse to the diagnosis of CNS metastasis was 9 months (range, 14 days to 42 months). This interval was ≤ 3 months in four patients (22%) and ≥ 12 months in eight patients (44%). Early-stage disease did not affect time to CNS relapse, with a median of 48 months for stage I compared with 44 months for stage II to IV patients.

All patients received at least one line of platinum-based chemotherapy. Eight (44%) of 18 patients received only one line of chemotherapy, three (17%) of 18 received two lines of chemotherapy, two (11%) of 18 received three lines of chemotherapy, and five (28%) of 18 received four lines of chemotherapy (Table 2). One patient developed CNS metastases while receiving first-line treatment, and three patients developed them within a month of completing fourth-line chemotherapy. The median (range) treatment-free intervals between each line of chemotherapy were 12 (2 to 42), 18 (5 to 31), and 4 (1 to 8) months, respectively. The response rates to chemotherapy were as follows: first line, 13 (72%) of 18 (three patients were nonassessable); second line, eight (80%) of 10; third line, three (43%) of seven; and fourth line, two (40%) of five.

Table 2. Results

Variable	Median (months)	Range (months)
Interval between diagnosis of ovarian cancer and first relapse	25.5	10-58
Interval between diagnosis of ovarian cancer and CNS metastases	46	12-113
Survival from diagnosis of CNS metastases	7	1-41
Treatment-free interval between each line of chemotherapy		
First and second	12	2-42
Second and third	18	5-31
Third and fourth	4	1-8

Survival

The median overall survival of patients from CNS relapse was 7 months (range, 1 to 41 months). In patients with both CNS and other sites of relapse, the median survival after the diagnosis of CNS disease was 5 months (range, < 1 to 27 months). In patients with CNS recurrence as the only site of disease, the median survival was 10 months (range, < 1 to 41 months). This difference was not statistically significant. All patients received corticosteroids, six underwent cranial radiation, one underwent surgery followed by radiotherapy, and two patients died before the intervention of any treatment.

Changing Incidence of CNS Relapse

The incidence of CNS metastases in our patient population was stratified into 5-year periods to analyze the changing incidence of metastasis at this site over time. In the period from 1980 to 1984, two (0.2%) of 945 patients were diagnosed with CNS metastases; from 1985 to 1989, none of 933 patients; from 1990 to 1994, three (0.3%) of 958 patients; and from 1995 to 1999, 11 (1.3%) of 854 patients. This trend of increased incidence was highly statistically significant ($P < .001$). Comparison of two published case series from the 1970s^{4,5} with two case series from the 1980s^{6,7} also suggests an increased incidence of brain metastases over this time ($P = .015$; Table 3).

DISCUSSION

In common with other reports, we have shown that CNS metastases are rare in patients with EOC; only 18 (0.49%) of 3,690 of our patients with EOC developed clinically apparent disease at this site. A limitation of this study is that histologic confirmation that brain metastases were of ovarian origin occurred in only two cases, raising the possibility that some of the lesions were either primary brain tumors or metastases from other occult primary tumors, eg, breast or lung carcinoma. This is a clear limitation of any study such

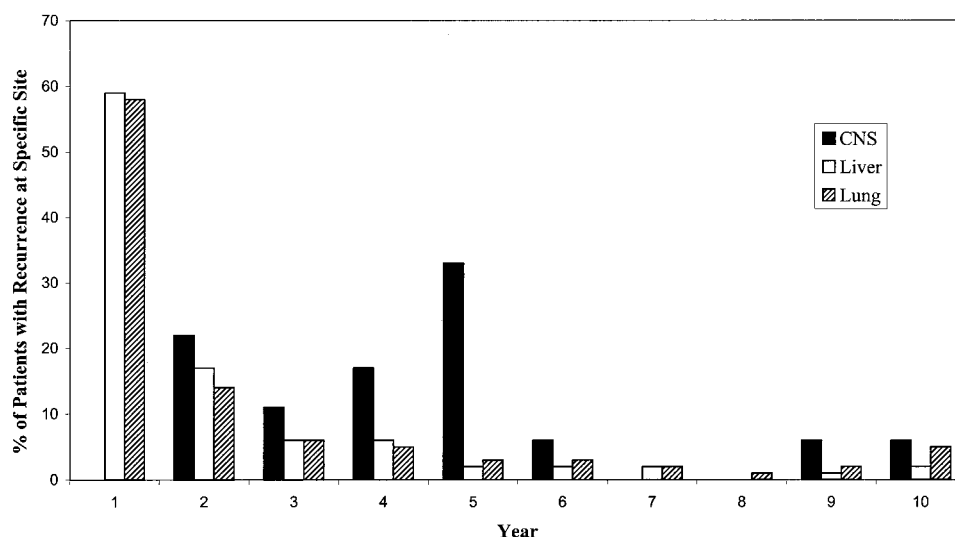


Fig 2. Year of relapse from diagnosis for patients with hematogenous metastases.

as this. This lack of histologic confirmation may be because there are often contraindications to brain biopsy in this clinical situation, and subsequent management is rarely significantly altered. Our finding that most patients with EOC and brain metastases have either poorly or moderately differentiated tumors is consistent with the experience of others.^{9,10} However, six (33%) of our patients originally had stage I disease, and this is rather unusual, because most studies have noted that EOC patients with CNS disease have had stage III or IV tumors at presentation.^{9,10} We did not find that these six patients had a statistically significant different time to CNS relapse when compared with advanced-stage patients who developed CNS secondary tumors (stage I, median 48 months; stage III to IV, median 44

months), and they had comparable survival, both overall and from the time of CNS recurrence.

In this article we have shown that the median time from diagnosis of ovarian cancer to documentation of CNS relapse is 46 months. This is a late time to relapse, particularly when compared with the time taken for hematogenous spread to other sites, such as liver and lung, where median time to relapse was approximately 6 months. This difference was highly statistically significant ($P < .001$). We have also demonstrated that nearly 40% of our patients received three or more lines of chemotherapy and that in a similar proportion of patients the treatment-free interval from the last treatment before CNS relapse was more than 12 months. Furthermore, nearly half of our patients (eight [44%] of 18) had the CNS as the only site of recurrent disease. These observations suggest that the CNS may be a sanctuary site from chemotherapy in EOC. This is analogous to the situation in the 1960s and 1970s with acute lymphocytic leukemia and, to some extent, Hodgkin's disease, in which CNS disease became a problem as more effective systemic treatments were developed and complete remissions were obtained.¹¹⁻¹³ The small but significant increase in the incidence of CNS metastases from EOC over the last 20 years is shown in our analysis of the literature and confirmed from our own data, which indicate a 10-fold increase in the last 5 years ($P < .001$). It should be noted that the absolute incidence of brain metastases in our series from 1980 to 1989 (two [0.1%] of 1,878 patients) is lower than that reported in the literature over roughly the same period. This difference is not easy to explain and may simply reflect the

Table 3. Incidence of Cerebral Metastases According to Date of Diagnosis

Reference	Years of Accrual	Total No. of Patients With Ovarian Cancer	No. of Patients With CNS Metastasis	Incidence (%)
Mayer et al ⁴	1973-1977	576	6	1.0
Barker et al ⁵	1969-1979	430	4	0.9
Rodriguez et al ⁶	1977-1990	795	15	1.9
Geisler and Geisler ⁷	1979-1992	479	16	3.3
Royal Marsden (2000)	1980-1984	945	2	0.2
	1985-1989	933	0	0
	1990-1994	958	3	0.3
	1995-1999	854	11	1.3

NOTE. Two patients were diagnosed in the year 2000 and were not included in this analysis.

nature of our study, ie, database derived, in contrast to the published literature, in which there may be reporting bias.

In summary, we describe a large cohort of patients seen over 20 years with EOC, in whom 0.49% had CNS metastases. We have demonstrated that CNS metastases in EOC are a rare and late manifestation of the disease, which occurs in patients with a prolonged survival caused by

repeated chemosensitive relapses. Our data suggest that CNS disease is occult in patients with EOC and that the brain may be a sanctuary site from systemic treatment. The incidence of metastasis at this site is still low, but as more effective systemic therapies are developed we can expect the incidence to increase, possibly to levels that may become clinically significant.

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