

CENTRAL NERVOUS SYSTEM METASTASES FROM PRIMARY EPITHELIAL OVARIAN CANCER

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Introduction

Epithelial ovarian carcinoma (EOC) is a common gynecologic malignancy in women.¹ Approximately two thirds of patients present with advanced disease. Debulking surgery followed by platinum-based chemotherapy is the standard treatment approach, and 15% to 30% of patients achieve long-term survival.² Relapse of disease in the pelvis, the abdomen, or both is the most common cause of failure.³ The central nervous system (CNS) is a rare site for metastasis. In this article, we report data on 18 such cases seen at our institution during the past 11 years. A systemic review of the English literature is also presented to assist the management of this interesting though still rare clinical problem.

Materials and Methods

Between January 1991 and December 2001, 785 patients with ovarian malignancy were registered in our Gynecology Tumor Clinic. The origin was epithelial in 658 of these cases, and CNS metastases were diagnosed at some time during follow-up in 18 (2.7%) of the 658 patients. The first 2 patients have been reported earlier.⁴ The characteristics of the patients are summarized in Tables 1 and 2. Baseline evaluation of these patients included the physical and pelvic examination, review of operative findings, hemogram and biochemistry results, review of histopathology, and radiography including computed tomography

(CT) scanning of the abdomen and pelvis, chest radiography, and serum CA-125 measurement. Patients received cisplatin-based chemotherapy using either cisplatin plus cyclophosphamide (CP),

Table 1. — Patient Characteristics (n=18)

Age (yrs):	
Median	54
Range	45 – 66.5
FIGO stage:	
I	1
IIIC	13
IV	4
Histology subtypes:	
Serous	13
Mucinous	2
Endometrioid	1
Poorly differentiated adenocarcinoma	2
Histologic grade (n=17):	
I	1
II	5
III	11
Primary treatment:	
Surgery/chemotherapy	12
Chemotherapy/surgery/chemotherapy	3
Surgery alone	1
Chemotherapy alone	2
Surgery type (n=13):	
Optimum	4
Suboptimum	9
Residual disease (n=13):	
None or <1 cm	4
>1 cm	9
Primary chemotherapy schedule (n=17):	
CP	4
CAP	8
Paclitaxel and carboplatin	3
CHAP	1
Other	1
Response to treatment (n=17):	
Complete response	8
Partial response	8
No response/poorly differentiated	1
CP = cisplatin, cyclophosphamide	
CAP = cisplatin, doxorubicin, cyclophosphamide	
CHAP = cisplatin, doxorubicin, cyclophosphamide, hexamethylmelamine	

cisplatin, doxorubicin, and cyclophosphamide (CAP), paclitaxel plus carboplatin (TC), cisplatin, doxorubicin, hexamethylmelamine, and cyclophosphamide (CHAP), or cisplatin alone. The diagnosis of CNS metastasis was based on abnormalities in either CT scans or magnetic resonance imaging (MRI) of the brain in 18 patients, surgical findings in 4 patients, and positive cerebrospinal fluid (CSF) cytology

in 3 patients. All patients with CNS metastasis were also evaluated for presence of any extracranial systemic disease. Patients who had an isolated solitary CNS metastasis underwent surgical resection followed by whole-brain radiotherapy (WBRT). The patients with multiple CNS metastases received WBRT, and patients who had extracranial disease also received systemic chemotherapy after WBRT.

underwent debulking surgery alone but refused chemotherapy.

CNS Metastases

The median interval from diagnosis of EOC and documentation of CNS metastases was 29 months (range 0 to 101 months). The median interval after completion of treatment for primary disease till documentation of CNS metastases was 19 months (range 0 to 56 months) (Table 2). The clinical presentation of patients included features of raised intracranial pressure (headache, nausea/vomiting, papilloedema) (10 patients), extremity weakness (9), seizures (3), vertigo (2), vision problems (2), tremors (2), aphasia (2), and altered consciousness (1). CT scans of the brain (Figs 1 and 2) revealed evidence of metastasis in the cerebrum in 13 patients, in the cerebellum in 2 patients, and in the cerebrum and cerebellum in 2 patients. One patient had meningeal involvement only.

Case #1: Of the 2 patients who had evidence of CNS metastases at initial diagnosis, 1 presented with diminished vision in the left eye. She was found to have choroidal metastasis. Further evaluation led to the finding of a pelvic mass and an asymptomatic, single cerebellar lesion. She received 6 cycles of cisplatin-based CT plus WBRT, which resulted in shrinkage of both the pelvic mass and the choroidal metastases. Laparotomy demonstrated a right ovarian tumor with deposits in the pouch of Douglas. The histology was a papillary serous adenocarcinoma.

Table 2. — Clinical Presentation and Interval to CNS Metastasis

	Median Interval (range)
Interval to CNS metastasis:	
From diagnosis of EOC	29 mos (0 – 101 mos)
After primary treatment	19 mos (0 – 56 mos)
	No. of Patients
Isolated CNS metastasis	5
Concurrent systemic disease	13
Peritoneal - 3	
Lung - 2	
Pelvis - 2	
Supraclavicular lymph node - 1	
>1 site - 5	
No. of metastases:	
Single	5
Multiple	12
Meningeal alone	1
Parenchymal and meningeal	2
Location:	
Cerebral	13
Cerebellar	2
Cerebral and cerebellar	2
Meningeal	1
Treatment for CNS metastasis:	
WBRT alone	8
Surgery + WBRT + chemotherapy*	4
Chemotherapy* + WBRT	5
Supportive treatment alone	1
WBRT = whole-brain radiotherapy	
* Chemotherapy regimens:	
tamoxifen + carboplatin (1),	
cisplatin + cyclophosphamide (2),	
carboplatin alone (1),	
carboplatin + oral VP-16 (1).	

Patient Characteristics

The median patient age at diagnosis of CNS metastases was 54 years (range 45 to 66.5 years). An analysis of the initial FIGO staging classification revealed 1 patient with stage I disease, 13 with stage III, and 4 with stage IV. Two of the 18 patients had CNS metastases at diagnosis. Serous papillary adenocarcinoma was the most common histology subtype (13 cases), followed by mucinous (2), poorly differentiated adenocarcinoma (2), and endometrioid (1). Eleven patients had grade III tumors, 5 patients had grade II tumors, and 1 patient had a grade I tumor. Thirteen patients had undergone primary debulking surgery followed by chemotherapy. Two patients with stage IIIC disease and 2 with stage IV disease had received neoadjuvant chemotherapy⁵ followed by interval debulking surgery. One patient who presented with CNS metastases with a pelvic mass

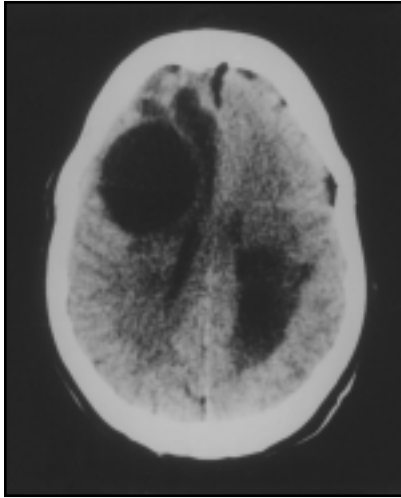


Fig 1. — Enhancing ring lesion in right parietal lobe with perifocal edema. Edema in the left parieto-occipital region is also present.

Postoperatively, she received 3 more cycles of chemotherapy. She is alive and disease-free.

Case #2: Another patient presented with weakness of her right arm and leg. MRI of the brain revealed multiple parenchymal metastases. She also had a large cystic pelvic mass. She underwent laparotomy with complete removal of an ovarian mucinous cystadenocarcinoma. She refused further treatment.

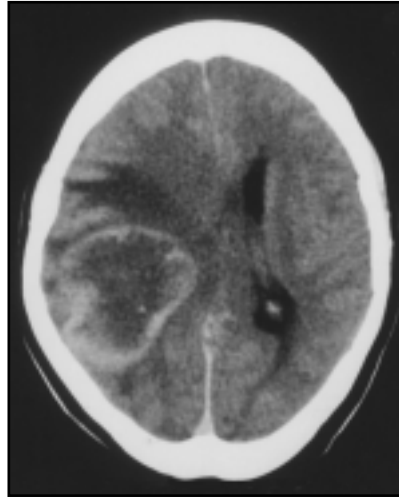


Fig 2. — Enhancing ring-like lesion seen in right parietal lobe with perifocal edema, with midline shift.

Another 2 patients who underwent laparotomy for primary ovarian cancer had seizures on postoperative days 3 and 5, respectively. CT scans of the brain revealed multiple cranial metastases in both patients, and the CSF was positive for malignant cells in 1 of them (Figs 3A-B).

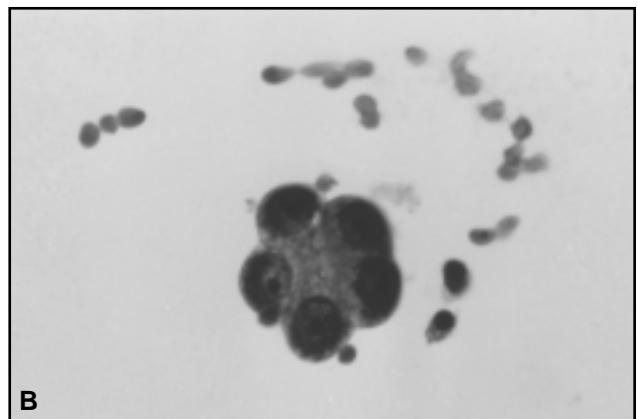
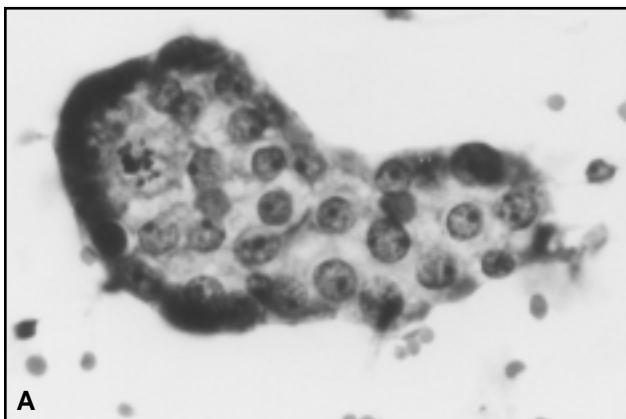
Five of the 18 patients had isolated CNS metastases. Thirteen also had evidence of systemic (extracra-

nial) disease located in the pelvis (2 patients), abdominoperitoneum (3), retroperitoneal lymph nodes (1), lung (2), and supraclavicular lymph node (1). Five patients had metastasis in more than one site. Brain imaging demonstrated that 5 patients had evidence of single CNS metastases and 12 patients had multiple CNS metastases. One patient had meningeal disease only, and 2 patients had both brain parenchymal and meningeal involvement.

Baseline serum CA-125 levels were estimated in 14 patients. Values were elevated in 11 (median 567 U/mL, range 150 to 2,191 U/mL). At the time of diagnosis of CNS metastasis, levels were elevated in 7 patients, with a median of 133 U/mL and a range of 116 to 800 U/mL.

Treatment for CNS Metastasis

Four patients with isolated single CNS metastasis underwent surgical excision of the metastasis. The histology was compatible with primary ovarian cancer. Surgery was followed by WBRT and



Figs 3A-B. — Photomicrographs of CSF positive for metastatic adenocarcinoma. (A) M66 \times 400; (B) Papanicolaou stain, \times 400.

chemotherapy. Eight patients received WBRT alone, 5 received chemotherapy plus WBRT, and 3 of the 5 also received intrathecal therapy, including the single patient

who had meningeal involvement only. One patient received supportive care only. Two patients in our study underwent gamma knife radiosurgery — 1 for the multiple

CNS metastases (4 metastases, 1 to 2 cm in diameter) and 1 for recurrent brain metastasis. Both had significant responses.

The median overall survival from diagnosis of CNS metastasis (data censored on June 30, 2002) was 4 months (range 1 to 74 months). The median overall survival from diagnosis of primary ovarian carcinoma was 30.5 months (range 5 to 110 months) (Figs 4 and 5). Currently, 7 patients are alive; 2 are disease-free at 4 and 12 months, respectively, and 5 patients are alive with disease at a median interval of 5 months (range 4 to 74 months). Two of these 5 have CNS disease, and the remaining 3 have both CNS and systemic disease and are currently on systemic therapy. Ten patients died of progressive disease, with a median interval of 3 months (range 1 to 10 months). Four deaths were due to uncontrolled CNS disease, and 6 died of the effects of extracranial systemic disease.

Prognostic Factors

We analyzed the data according to patient characteristics and treatment type (Table 3). Patients with serous histology had a better survival ($P < .02$) than those with a nonserous histology. Those with grade I or II tumors survived longer than those with grade III tumors (10 months vs 3 months; $P = .23$). Improved survival was also observed in those who had optimal rather than suboptimal surgery (10 months vs 4 months; $P = .37$). There was also a suggestion (not statistically significant) that those with minimal residual disease lived

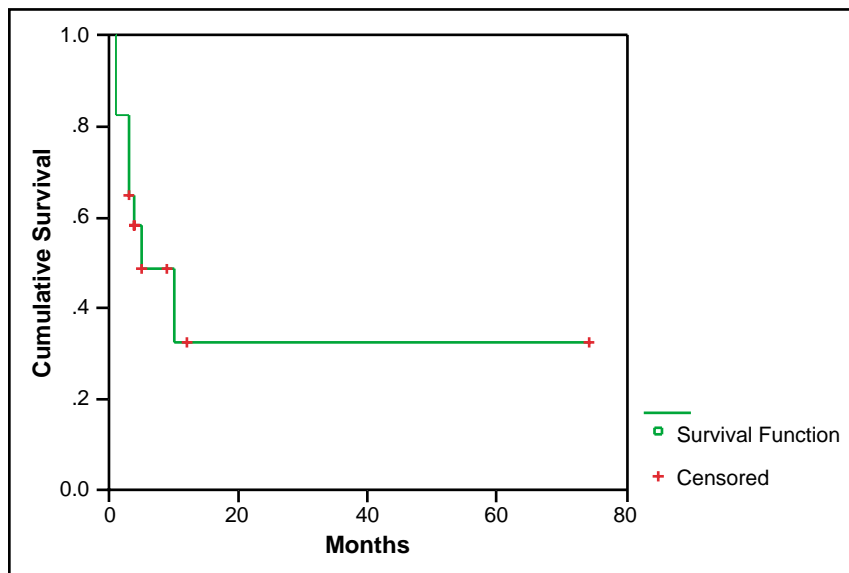


Fig 4. — Overall survival after diagnosis of CNS metastasis.

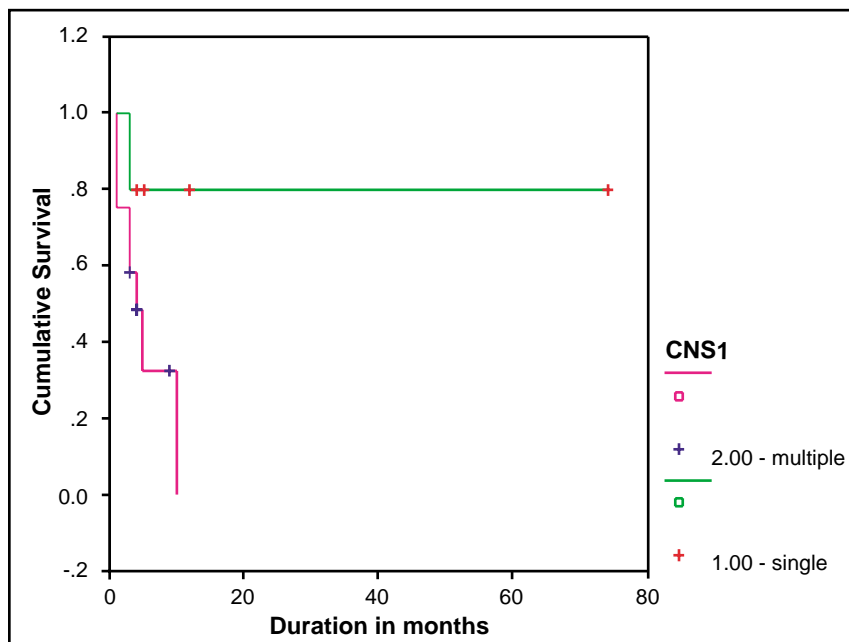


Fig 5. — Overall survival according to number of CNS metastases.

longer than those with gross residual disease (10 months vs 4 months; $P=.19$). Patients with concurrent extracranial disease had a poorer prognosis than those with isolated CNS metastasis ($P<.07$). For patients with multiple brain metastases, the median survival was 4 months. Median survival has not yet been reached for patients with a single brain metastasis ($P<.06$). The median overall survival for patients treated with WBRT alone was 3 months but has not yet been reached for patients

treated with surgery plus WBRT and CT or for those treated with WBRT and CT ($P=.23$).

Review of the Literature

We combined the data on our 18 patients with 190 patient cases reported in the English literature.^{4,6-59} An incidence rate for CNS metastasis from EOC of 1%, ranging from 0.49% to 2.2%, has been reported in the literature (Table 4). The median age at presentation was 54.5 years

(range 31 to 79 years). The median interval from diagnosis of EOC to CNS metastasis was 21.5 months (range 0 to 126 months). In 8 patients (4%), CNS involvement either preceded or was simultaneous with the diagnosis of ovarian carcinoma.^{17,19,27,29,36,38,51}

Stage, Histopathology, and Grade of Primary Tumor

Seventy-seven percent of patients had FIGO stage III or IV (Table 5). Serous histology was the most common subtype (68%), followed by endometrioid, adenocarcinoma, undifferentiated carcinoma, mucinous, and clear cell. Tumor grade III (61%) was most common, followed by grade II (35%). Only 4% of patients had a grade I tumor.

CNS Metastasis

There was evidence of both CNS and extracranial disease in 63.8% of patients, while 36% of patients had an isolated CNS relapse. Of these, 42.6% had solitary metastasis, 50.1% had multiple metastases, and 6.3% had meningeal involvement. The cerebral hemisphere was the most common site of metastasis (75%), followed by the cerebellum (11%). The falx cerebri and spinal cord³ are occasional sites for metastases (Table 6). The distribution of cerebral metastasis included the parietal lobe, the frontal lobe, and the temporal lobe, in order of decreasing frequency.

CNS Presentation

Raised intracranial pressure was the most common presenting

Table 3. — Analysis of Prognostic Factors

Prognostic Factor	No. of Patients	Median Survival (mos)	P Value
Histology:			
Serous	12	10	<.02
Others	5	1	
Grade:			
I or II	6	10	.23
III	11	3	
Surgery (n=13):			
Optimum	4	10	.37
Suboptimum	9	4	
CT regimen:			
CAP	8	10	.24
Others	9	3	
Response to primary CT:			
Complete response	8	10	.68
<Complete response	9	3	
No. of CNS metastases:			
Single	5	*	.06
Multiple	12	4	
Concurrent systemic disease:			
Yes	13	3	.07
No	5	>4	
CNS treatment:			
Surgery + WBRT+ CT	4	* (mean OS = 23.3)	.23
WBRT alone	8	3	
CT + WBRT	5	* (mean OS = 6.3)	

WBRT = whole-brain radiotherapy
OS = overall survival
CT = chemotherapy
CAP = cisplatin, doxorubicin, cyclophosphamide
* Median not reached.

Table 4. — Incidence Rate of CNS Metastasis in Primary Ovarian Cancer

Author	Study Period	No. of Patients With EOC	No. of Patients With CNS Metastases	Incidence (%)
Mayer ⁹ (1978)	1973-79	576	6	1.0
Barker ¹¹ (1981)	1969-79	430	4	0.9
Piura ³² (1990)	1961-88	200	2	1.0
Rodriguez ²⁶ (1992)	1977-90	795	15	1.9
Bruzzone ⁴⁰ (1993)	1981-89	413	9	2.2
Cooper ⁴² (1994)	1987-92	230	3	1.3
Corn ⁴⁷ (1995)	1965-94	4,027	32	0.8
Kaminsky-Forrett ⁵⁴ (2000)	1974-98	704	8	1.1
Anupol ⁵⁷ (2002)	1986-00	1,042	15	1.4
Kolomainen ⁵⁸ (2002)	1980-99	3,690	18	0.49
Present study	1991-2001	658	18	2.73
Total		12,765	130	1.01

Table 5. — Stage, Histology Subtype, and Stage of Primary Tumor

	No. of Patients		Total	%
	Literature	Present Study		
FIGO stage:				
I	20	1	21	10.8
II	24	0	24	11.9
III	110	13	123	57.2
IV	36	4	40	20.1
Total	190	18	208	100.0
Histology subtype:				
Serous	64	13	77	68.1
Mucinous	2	2	4	3.6
Endometrioid	13	1	14	12.4
Clear cell	1	0	1	.9
Undifferentiated	5	1	6	5.3
Adenocarcinoma	10	1	11	9.7
Total	95	18	113	100.0
Grade:				
I	5	1	6	3.7
II	50	5	55	34.4
III	88	11	99	61.9
Total	143	17	160	100.0

symptom (38.8%), followed by neurological weakness (23.5%), seizures (11.2%), speech impairment (5%), and vision problems (4%). Bladder/bowel involvement was most common with meningeal metastases. All of the patients presenting with coma died within 2 days to 2 weeks of diagnosis.

Among patients with evidence of recurrent extracranial disease at the time of CNS metastases, the most common sites of failure were in the pelvis, abdominoperitoneum, liver, lungs, and lymph nodes.

Treatment of CNS Metastasis

Patients with an isolated solitary CNS metastasis generally underwent craniotomy with metastasectomy followed by WBRT. Patients with multiple CNS metastases with or without extracranial disease received WBRT with or without systemic chemotherapy. Some patients with poor general condition received only supportive care in the form of corticosteroids, mannitol, and antiepileptic agents. Radiotherapy doses ranged from 30 to 40 Gy to the whole brain in multiple fractions. Chemotherapeutic drugs used included cisplatin, carboplatin with or without cyclophosphamide, and doxorubicin.

Survival

The median overall survival after diagnosis of CNS metastases was 7.2 months, ranging from 2 days to 76 months. The median

Table 6. — CNS Metastasis: Number and Sites

	No. of Patients		Total	%
	Literature	Present Study		
No. of CNS metastases:				
Single	82	5	87	42.6
Multiple	92	12	104	51.0
Meningeal alone	12	1	13	6.4
Total	186	18	204	100.0
Sites:				
Cerebral	110	13	123	75.0
Cerebellar	16	2	18	11.0
Cerebral + cerebellar	6	2	8	4.9
Meningeal	11	1	12	7.3
Falx cerebri	1	0	1	0.6
Spinal cord	2	0	2	1.2
Total	146	18	164	100.0

overall survival was higher for patients treated with surgery plus WBRT and CT compared to those treated with WBRT alone, (14.5 months vs 5.5 months). For patients treated with supportive care only, the median survival was 1.5 months (range 2 days to 5 months) (Table 7).

Discussion

While CNS metastasis from primary solid tumors⁶⁰ (eg, small-cell lung cancer,⁶¹ breast,⁶² prostate,⁶³ germ cell tumors,^{64,65}) is well known, CNS metastases from primary EOC are rare. We identified 18 such cases among 658 patients (2.73%) seen over an 11-year period. In an autopsy study of 567 women with EOC, Mayer et al⁸ identified 5 cases of CNS metastases (0.9%). Similarly, other studies have reported an incidence of 0.9% to 2.2% in hospital-based studies among patient populations ranging from 430 to 4,027.^{11,32,36,40,42,47,54,57} A recent study from the Royal Marsden Hospital in the United King-

dom identified 18 patients (0.49%) among 3,690 patients with EOC over a 20-year period (Table 4).⁵⁸ There was a trend for a higher incidence between 1995 to 1999 (1.3%) compared to 1980 to 1994 (range 0% to 0.3%). Possible reasons for the increased incidence of CNS metastasis that has been reported during the past 3 decades include changes in the biology of EOC due to better control of abdominopelvic disease with cisplatin-based chemotherapy resulting in longer survival and the availability of better imaging techniques (CT scan/MRI scan of brain) for diagnosing CNS metastasis.^{29,40} Metastasis to the CNS from primary

EOC has been postulated to occur via direct hematogenous seeding through Virchow-Robin perivascular spaces, retrograde lymphatic spread for meningeal involvement, or direct invasion into CNS after bony involvement.

In our series of 18 patients, the median age of 54 years at diagnosis of CNS metastases is similar to that previously reported. Two of 18 patients had evidence of CNS metastases at initial presentation. Only 8 such cases have been described previously.^{17,19,27,29,36,38,51} For the others, the median interval from diagnosis of EOC to development of brain metastases was 29 months (range 18 to 101 months), and the median interval after completion of treatment to CNS metastases was 19 months. These observations are similar to earlier reports. Two important findings in our study were the presence of stage III or IV disease in 94% of patients and the finding of grade III tumors in 65% (Table 1). Higher stage and higher grade of primary tumor have also been reported consistently in previous studies (Table 5). These findings suggest that higher stage and higher grade are associated with an increased

Table 7. — Treatment of CNS Metastasis

Treatment	No. of Patients	Median Survival	Range
Surgery ± radiotherapy	35	15.5 mos	2 – 45 mos
Radiotherapy + chemotherapy	34	7.2 mos	1 – 76 mos
Radiotherapy alone	45	5.5 mos	1 – 26 mos
Surgery + radiotherapy + chemotherapy	18	14.5 mos	3 – 48 mos
Supportive care alone	21	1.5 mos	2 days – 5 mos
Total	153	7.2 mos	2 days – 76 mos

risk of brain metastasis. There was no correlation between an increased risk of CNS metastases with type of chemotherapy used (CP vs CAP or paclitaxel plus carboplatin) or with response to primary chemotherapy (complete vs partial). Patients with suboptimum debulking, and consequently gross residual disease, were at a greater risk for developing CNS disease. However, this finding was not statistically significant (Table 3).

The most common presentations for the patients are symptoms from raised intracranial pressure with or without focal neurological deficit, followed by seizures or vision or speech symptoms. On CT or MRI scan of brain, diagnosis of CNS metastasis becomes obvious in most cases, although we saw 1 patient in whom both the CT scan and the MRI were normal. CSF examination for malignant cells confirmed the presence of meningeal carcinoma.

The therapy of CNS disease depends on the presence or absence of extracranial disease and single vs multiple brain metastases. Traditionally, for patients with isolated CNS disease — with single and/or resectable metastases — surgical resection followed by WBRT and systemic chemotherapy is a viable option. This approach is superior to WBRT alone and is associated with longer overall survival, longer duration of neurological improvement, and decreased risk of recurrence.⁶⁶⁻⁶⁸ Results from our study and from those in the literature confirm these observations (Table 7).

For patients with multiple brain metastases, WBRT with or without chemotherapy remains the treatment of choice. Poor penetration of the blood-brain barrier is considered to be a limiting factor for routine use of systemic chemotherapy. Recent studies with systemic chemotherapy have shown objective responses with improved survival for patients with CNS metastases among patients with primary breast cancer and germ cell tumor.⁶⁹ Objective responses and survival benefit have also been documented even in patients with primary EOC.^{32,35,36,42,45,48} Cooper et al⁴² treated 3 patients with CNS metastases from primary EOC using carboplatin alone. In 1 patient with a single lesion, complete resolution was achieved, and in the other 2 patients, a significant reduction in tumor mass occurred. In our study, the mean survival is better for patients treated with WBRT plus chemotherapy than for those treated with WBRT alone (6.3 months vs 3.6 months). The median survival for patients treated with WBRT plus chemotherapy has not yet been reached. Similarly, a review of the literature shows a median survival of 7.2 months vs 5.5 months for patients treated with CT and radiation therapy vs radiation therapy alone (Table 7). The presence of concomitant extracranial disease in 72% of our cases and in 63.8% of patients in the literature review would further argue in favor of use of systemic chemotherapy. This may help to control extracranial disease and may improve overall median survival. These results need to be interpreted with caution, however,

as patients receiving chemotherapy might be in better performance status compared to those who receive WBRT alone.

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