Review

Brain Metastases from Epithelial Ovarian Cancer: Overview and Optimal Management*

KLAUS PIETZNER[1], GUELTEN OSKAY-OEZCELIK[1], KHALID EL KHALFAOUI[1], DIRK BOEHMER[2], WERNER LICHTENEGGER[1] and JALID SEHOULI[1]

[1]*Department of Gynaecology and Obstetrics,* [2]*Department of Radiation Oncology and Radiotherapy, Charité-Campus Virchow Klinikum, Medical University of Berlin, Berlin, Germany*

Abstract. *Central nervous system involvement is a rare finding in the management of epithelial ovarian cancer with an incidence between 1-2% . A sharp rise in the incidence has been widely and repeatedly proclaimed for nearly two decades now, but has to be treated with scepticism after a careful review of the current literature. Brain metastases from ovarian cancer are known to be related to a very poor prognosis. Since brain imaging is not part of the routine follow-up care for ovarian cancer patients, and since CA-125 – one of the standard tools – cannot be relied upon to detect central nervous system relapse, brain lesions are mostly traced by unspecific neurological symptoms only. Several prognostic factors are still being discussed today. But only a high performance status and the absence of an extra cranial disease at the time of CNS relapse have been accepted throughout the current literature as having a highly significant positive impact on survival. In the past, therapeutic efforts have focused on symptom palliation with corticosteroids and whole-brain radiation therapy (WBRT). During the last years several other therapy options have evolved from encouraging efforts made by several study groups, including chemotherapy, neurosurgery and radiosurgery. It has been shown that a multi-modal approach, combining these strategies, promises the best prolongation of survival and in some cases even resulted in long-term remissions. The present article gives an overview of brain metastases in epithelial ovarian cancer and discusses the current treatment options.*

Brain metastases are a common but severe complication in the field of oncology. Approximately 20-40% of all cancer patients will develop brain metastases during their course of disease, with breast cancer, lung cancer and melanoma representing the most common primary malignancy (1). The occurrence of brain lesions is usually associated with a grim prognosis in these diseases and an overall survival rate of 1-2 months only (1). The standard treatment consists of whole-brain radiotherapy (WBRT), which was shown to improve the quality of life by a reduction of neurological symptoms and seems to result in a prolongation of survival to 3-6 months (2, 3). Patients with a good performance status, a controlled extra-cranial disease and a single brain lesion are those generally considered for more aggressive unimodal or multimodal therapy strategies, including surgical resection, stereotactic radiosurgery (SRS), postoperative radiation, various radiotherapy dose fraction schedules and chemotherapy. These therapy options are mostly incorporated into established guidelines, due to the common occurrence of central lesions in these malignancies. Brain metastases from epithelial ovarian cancer (EOC) on the other hand are a very rare finding in the gynaecological-oncological setting. Because of the likewise poor prognosis and limited experience with this complication in the management of EOC, the question has been raised in the past whether or not these patients should be submitted to any form of therapy apart from the administration of corticosteroids. Studies which have been conducted in response were able to demonstrate that patients with CNS relapse from EOC do benefit from any kind of interventional therapy (radiation, surgery, chemotherapy) when compared to

*Presented at the 8th International Conference of Anticancer Research, 17-22 October 2008, Kos, Greece.

This work was presented in part at the VII International Symposium of the North-Eastern German Society of Gynecologic Oncology (NOGGO) at the 8th International Conference of Anticancer Research 2008.

Correspondence to: Professor Dr. Jalid Sehouli, MD, Department of Gynaecology and Obstetrics, Charité-Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30450564235, Fax: +49 30450564928, e-mail: sehouli@aol.com

Key Words: Brain metastases, ovarian cancer, central nervous system relapse, brain lesions, review.

Table I. *Incidence of brain metastases from epithelial ovarian cancer.*

Author and year of publication	Duration of study	No. of patients with EOC	Incidence (%)
Cohen *et al*. 2004 (7)	1975-2001	68	1.0
Corn *et al*. 1995 (13)	1965-1994	32	0.9
Kolomanien *et al*. 2002 (14)	1980-1999	18	0.5
Kumar *et al*. 2003 (15)	1991-2001	18	0.7
Pectasides *et al*. 2005 (16)	1983-2004	17	1.2
Geisler *et al*. 1995 (8)	1979-1992	16	3.3
Rodriguez *et al*. 1992 (6)	1977-1990	15	1.9
Anupol *et al*. 2002 (2)	1986-2000	15	1.4
Le Roux *et al*. 1990 (17)	1980-1990	14	1.1
Larson *et al*. 1986 (18)	1944-1984	13	0.3
Kim *et al*. 2007 (9)	1996-2005	13	2.7
Cormio *et al*. 1996 (12)	1982-1994	10	0.9
Li *et al*. 2003 (19)	1996-2001	10	2.1
Bruzzone *et al*. 1993 (20)	1981-1989	9	2.2
Kaminsky-Forret *et al*. 2000 (21)	1974-1998	7	1.1
Ross *et al*. 1988 (22)	1980-1984	7	1.9
Hardy *et al*. 1989 (23)	---	6	11.6
Mayer *et al*. 1978 (5)	1973-1979	6	1.0
Stein *et al*. 1986 (24)	1979-1985	5	4.5
Dauplat *et al*. 1987 (25)	---	5	2.0
Tay *et al*. 2005 (26)	1993-2003	4	0.7
Barker *et al*. 1981 (27)	1969-1979	4	0.9
Cooper *et al*. 1994 (28)	1987-1992	3	1.3
Budd *et al*. 1983 (29)	---	3	7.1
Charité Multicenter Study (30)	1981-2008	72	1.7

Including studies with collectives of 3 patients or more.

Table II. *Incidence of single vs. multiple brain metastases in ovarian cancer.*

Author	No. of patients	Single lesion (%)	Multiple lesion (%)
Kim *et al*. 2007 (9)	13	15	85
Cohen *et al*. 2004 (7)	73	35	65
Anupol *et al*. 2002 (2)	15	50	50
Geisler *et al*. 1995 (8)	16	50	50
Cormio *et al*. 1995 (12)	23	49	51

treatment with corticosteroids only (4). In the last years, more and more therapy options have evolved from the experience with brain metastases in other malignancies and have been put into effect to challenge this complication in the management of ovarian cancer. Different meta-analyses of larger patient collectives have reported that a multimodal approach yields the best results in terms of reduction of neurological symptoms and prolongation of survival (3, 4). This review is intended to present the different therapeutic options and their individual values to patients with brain metastases from EOC, as well as to provide an overview of this uncommon condition.

Incidence

Brain metastases from ovarian cancer have traditionally been considered to be a very rare form of relapse since its first description in 1978 by Mayer *et al*. (5). In their autopsy report of 567 cases between 1973 and 1979, they found an incidence of 0.9%. After this first report, subsequent investigators reported a higher incidence of 1-2.5% (6-8). This rise in incidence has been contributed to several factors. The most plausible one reflects the advances and increased availability of imaging techniques, leading to an earlier and more sensitive diagnosis of brain lesions. Another factor is stated to be the prolonged survival achieved by better therapy regimens including more aggressive cytoreductive surgery and systemic chemotherapy. This results in brain metastases being a variation of the basic disease, a finding that was not possible 20 years ago because of the short time interval between first diagnosis and death. Other theories claim a connection to modern chemotherapy and the blood-brain barrier (BBB), stating either that cancer cells can implant more easily through an impaired BBB after chemotherapy, or that the BBB acts as a safe haven from chemotherapeutic agents.

There are several authors who state that the incidence of CNS relapse in ovarian cancer is rising even more rapidly during the last years and is approaching 12%. However, after a careful review of the current literature, reports of an incidence over 2.5% are the exception and limited only to a few articles which are now mostly outdated. Even though these reports are often cited in current articles as proof of an ongoing sharp rise in incidence, most of the authors who studied larger collectives in the last years reported a stable incidence between 1-2.5% (Table I). Despite the fact that the incidence reported has not changed rapidly in the last decades, 1-2.5% is most certainly still a strong underestimate of the true figure. This is due to the fact that nearly all articles published on this subject are clinical studies rather than autopsy studies. Because brain imaging is not part of the routine follow-up care of ovarian cancer patients, the reported incidence of 1-2.5% is more likely a figure just below the rate of symptomatic brain lesions in ovarian cancer, given that the often unspecific symptoms will not always result in further diagnostic steps.

Site and Appearance of Metastatic Manifestation

Metastases from EOC can present themselves in a variety of phenotypic manifestations (Figure 1). The tumour lesions can be solid, cystic and mixed, whereas mixed solid-cystic seems to be the most common form. At the time of CNS relapse from ovarian cancer, the number of patients with a single brain lesion and multiple lesions is balanced in most

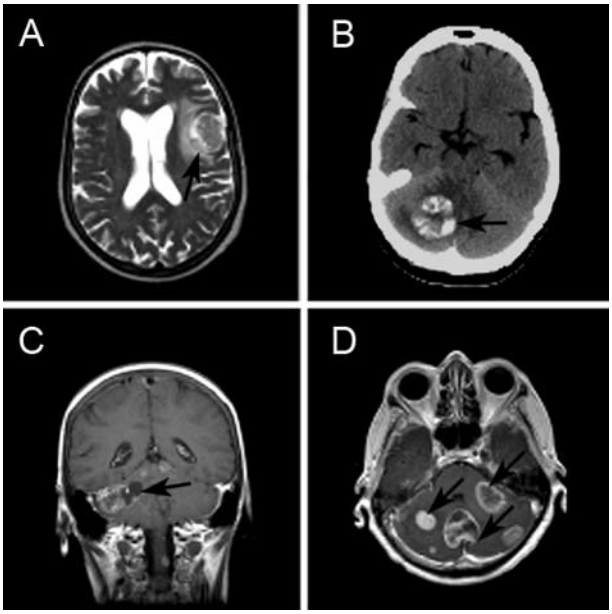

Figure 1. *Cranial images of patients with brain metastases from ovarian cancer diagnosed at Medical University of Berlin. A, Axial magnetic resonance (MR) imaging of the brain (T2-weighted) showing a prominent tumor in the left parietal lobe with low density signal surounding the tumor mass representing an edema. B, Axial enhanced CT scan of the brain showing 33 mm right inhomogeneous cerebellar lesion with perifocal edema. C, Frontal MR imaging of the brain (T1-weighted) demontrates a right inhomogeneous cerebellar lesion with surrounding focal edema. D, Axial MR imaging of the brain (T1-weighted) demonstrates different inhomogeneous signal density compatible to multiple metastatic cerebellar lesions.*

reports (2, 8). However, there seems to be a trend towards multiple lesions being the more common form of presentation, as currently reported by several authors (Table II) (7, 9). This observation is in concordance with experience from other malignancies such as lung cancer and melanoma. In these carcinomas, which regularly cause brain metastases, multiple brain lesions occur more frequently than they do in ovarian cancer (10). In terms of regional distribution, the frontal lobe was reported to be the most frequent localisation of metastatic manifestation, followed by the parietal lobe, the temporal lobe and the cerebellum (11). At time of diagnosis of brain metastases, proof of extra cranial disease is found in over half of the patients.

Clinical Criteria of Patients with Brain Metastases from EOC

The mean age at diagnosis of brain metastases from ovarian cancer ranges from 54-56 years (6, 17, 18). This seems to be lower than the classical mean age of ovarian cancer patients which is between 59 and 62 years. About 80% of the patients had a FIGO stage III or IV when first diagnosed as having EOC, whereas only the remaining 20% had FIGO stage I and II (3). The most common histology is the serous type, which is found in over half of the cases. This is followed by mixed epithelial, endometrioid, adenocarcinoma, mucinous, undifferentiated and clear cell histology, all in decreasing frequency (3). This sequence is not surprising, because investigators could not identify any histological type that increases the risk to develop brain lesion and because of the fact that the serous type is the most common histological type in ovarian cancer. Undifferentiated primary tumours are reported far more often in EOC patients than differentiated ones are, with undifferentiated malignancies being found in 68% (grades III and IV), and differentiated tumours in only 32% (grades I and II) (3). Cohen *et al*. reported a median time from primary diagnosis to development of cerebral lesions of 4.7 years in patients with tumour grades I and II *versus* 1.5 years in patients with tumour grade III (7). LeRoux *et al*. on the other hand reported that the interval between primary diagnosis and occurrence of brain relapse is five times shorter in patients with stages III and IV, than it is for stages I and II (17). These findings add to the assumption that patients with undifferentiated primary tumours and advanced disease at the time of first diagnosis of EOC have a higher risk of developing brain lesions.

Prognostic Factors

In the last few decades many investigations have been performed in order to gain a better understanding of ovarian cancer metastatic to the brain. One of the main perspectives of these efforts has been to identify prognostic factors for the survival of these patients. Many different factors have been investigated but partly with conflicting results. Only two factors were able to achieve acceptance by most authors of the current literature. One factor is the presence of extra-cranial disease at the time of brain relapse, which was shown to have a significantly negative impact on survival. Anupol *et al*. reported a median survival of 8 months for the occurrence of brain lesions for patients without any evidence of extracranial disease, in comparison to 3 months for cases which did yield that evidence (p=0.005) (2). Cohen *et al*. affirmed these findings and reported a median survival of 12.2 *versus* 3.5 months (p=0.001) (7). The other independent factor is the performance status of the patients at the time of recurrent disease. It was shown that a high performance status is likewise related to a higher median survival from the time of central metastatic relapse (31).

For the factors "single" *versus* "multiple" metastases and the time interval between primary diagnosis and metastatic manifestation, no consistent conclusion can be drawn from the recent literature because the results are not significant in multivariate analysis. A solitary lesion most likely promises

a slight advantage over presentation with multiple lesions, as reported by Anupol *et al*. with a median survival of 7 *versus* 5 months (p=0.07), but this factor does not withstand multivariate analysis in most reports (2). A short time interval between primary diagnosis and brain relapse was reported to have a negative impact on survival. Cormio *et al*. for instance found a median survival of 9 months for patients with an interval shorter than 40 months *versus* a median survival of 16 months for patients with a longer interval (p=0.03) (12). But again, this factor did not pass multivariate analysis. On the other hand, for most of the other factors which have been investigated in the past, like tumour stage, grade, histotype, age at diagnosis of CNS relapse, and site of lesion, it is widely agreed upon in the current literature that these are not related to survival (12).

Therapeutic Options

Therapeutic options for patients with brain metastases from EOC include best supportive care with or without corticosteroids, surgery, radiation (including SRS) and chemotherapy. Death in these patients often results from cranial herniation in the wake of highly increased intracranial pressure. This can be due to large, mostly cystic lesions causing a mass effect, or due to a cerebral oedema surrounding the lesions. A therapeutic approach to this problem is the treatment with corticosteroids, which often results in a satisfactory symptom reduction. However, it was shown by McMeekin *et al*. that this treatment is of strictly palliative nature and is equivalent to no treatment in terms of mortality, whereas any other form of therapy (radiation, surgery, gamma-knife, chemotherapy), not focusing on the treatment modality, does translate to a prolongation of median survival from 2 to 7 months (4). When compared with each other individually, the conventional neurosurgical approach promises the best results. Even though success of surgical therapy options is often boosted by selection bias, there is evidence that surgery is the most promising individual technique when applicable in the individual patient. Despite that fact, the most commonly used individual therapy strategy is WBRT. This is mostly due to contraindications to surgery, inaccessibility of lesions and the presence of multiple metastases. WBRT applied individually has the potential to decrease neurological symptoms and prolong median survival up to 3-6 months (7, 21). The technique is easily applicable to most patients, even with multiple and otherwise inaccessible lesions, but can cause severe dementia and brain atrophy (in case the patient lives long enough to experience late sequelae).

Even though chemotherapy is an inherent part of standard treatment for ovarian cancer and even extracranial recurrence, its role in the treatment of brain metastases still remains somewhat controversial with regards to the management of EOC. Case reports have shown good results and even complete remission with platinum-based agents such as carboplatin and cisplatin (32, 33). There are very few reports on any experience with chemotherapy as an individual therapeutic strategy. Melichar *et al*. reported a median survival of 16 months after chemotherapy alone, while other studies observed a median survival of 11-15 months only, even when combined with surgery or radiation (3, 6, 31). Up to this point there is not enough evidence on individually applied chemotherapy, and further trials are needed to support promising results. Also, the focus in future studies should shift towards agents with the potential of reaching a high concentration in the cerebrospinal fluid, because of their ability to cross the BBB. Most agents of platinum-based chemotherapy – the standard choice for ovarian cancer – do not possess this potential (34). Cisplatin for example reaches only a mere concentration of 0-2% compared to the blood level, while agents like topotecan can achieve a concentration of up to 40% (34, 35). Even although it is known that the BBB is already impaired in the metastatic lesion itself, there is experience, from other malignancies frequently causing brain metastases, which favours agents with that potential (36). Although an individual therapy strategy has benefits because of simple application and limited side-effects, many investigators have proven that the therapeutic potential can be greatly increased by the combination of different modalities into a multimodal approach. Cohen and colleagues report a median survival of 5.6 months for surgery or WBRT when these are employed individually, but they also observed a multiplication of the median survival to 23.1 months after a combination of both strategies (7). Great efforts have been undertaken to identify the optimal combination of modalities, but the results remain to a certain extent a matter of dispute. Two strategies have evolved as most promising from studies with large collectives and meta-analysis. One is the combination of surgery and radiation, the other a threefold approach with additional chemotherapy. Pectasides *et al*. reported a median survival of 21 months after treatment with surgery plus radiotherapy *versus* 20 months with additional chemotherapy (16). Melichar *et al*. on the other hand observed a median survival of 17 months after surgery and radiotherapy compared to 20 months after a triple therapy with added chemotherapy (31). Anupol *et al*. found a median survival of 16 months after radiation plus surgery *versus* 22 months after added chemotherapy (2). However, this benefit achieved through additional chemotherapy has to be weighed against the potential side effects of this option. Even though chemotherapeutical agents are usually well tolerated, a number of frequent side effects are known to exist. These effects might not pose a great threat, but most chemotherapy-related side-effects result in a decrease of quality of life for the patient. Considering that brain relapse in ovarian cancer is generally a palliative situation, quality of life should be one of the main objectives that has to be taken into account in the

decision on the optimal therapy strategy. In the last few years SRS (for instance linear accelerator- or gamma-knife-based) has come into focus as another promising therapy option in brain metastases from ovarian cancer. SRS is mostly applied in patients with no more than 3 cerebral lesions, which are treated with one single high-dose radiation fraction. Lee *et al*. even observed a remarkable median survival of 29 months after treatment with SRS compared to 6 months after WBRT (37). Few investigators have combined this option with other strategies, despite its promising properties. Even though the findings of Lee *et al*. might be subject to selection bias, SRS is a very promising option that should be further investigated in future trials and integrated into a multimodal approach.

Conclusion

The outcome of patients with brain metastases from EOC is very poor, having an overall survival from diagnosis of CNS-lesions of about 7 months only (4). A multimodal therapy approach may achieve an improved outcome for the patients and should therefore be utilized whenever applicable. The evidence available to date is pointing towards a combination of surgery and radiotherapy as the treatment modality with the best benefit to drawback ratio (3). An additional chemotherapy can potentially improve clinical outcome in some patients, but this benefit has to be measured against possible side-effects. Further research is needed to clarify the value of chemotherapeutic agents having a potential of reaching high concentrations in the cerebrospinal fluid in patients with brain relapse from EOC. Even though it is known that the BBB is already impaired in metastatic lesions, there is some evidence that agents with that potential have a higher impact on tumour reduction (36). A promising strategy for the future might be an increased employment of the stereotactic radiosurgery, with its capability to remove lesions inaccessible to neurosurgery with an efficiency equivalent to surgical resection (37). Future studies should focus on the integration of stereotactic radiosurgery into the multimodal approach, in order to obtain optimal surgical tumour removal even in patients with multiple lesions prior to any application of chemotherapy.

References

1 Wong J, Hird A, Kirou-Mauro A, Napolskikh J and Chow E: Quality of life in brain metastases radiation trials: a literature review. Curr Oncol *15(5)*: 25-45, 2008.

2 Anupol N, Ghamande S, Odunsi K, Driscoll D and Lele S: Evaluation of prognostic factors and treatment modalities in ovarian cancer patients with brain metastases. Gynecol Oncol *85(3)*: 487-492, 2002.

3 Pectasides D, Pectasides M and Economopoulos T: Brain metastases from epithelial ovarian cancer: a review of the literature. Oncologist *11(3)*: 252-260, 2006.

4 McMeekin DS, Kamelle SA, Vasilev SA, Tillmanns TD, Gould NS, Scribner DR, Gold MA, Guruswamy S and Mannel RS: Ovarian cancer metastatic to the brain: what is the optimal management? J Surg Oncol *78(3)*: 194-200, 2001.

5 Mayer RJ, Berkowitz RS and Griffiths CT: Central nervous system involvement by ovarian carcinoma: a complication of prolonged survivial with metastatic disease. Cancer *41(2)*: 776-783, 1978.

6 Rodriguez GC, Soper JT, Berchuck A, Oleson J, Dodge R, Montana G, Clarke-Pearson DL: Improved palliation of cerebral metastases in epithelial ovarian cancer using a combined modality approach including radiation therapy, chemotherapy, and surgery. J Clin Oncol *10(10)*: 1553-1560, 1992.

7 Cohen ZR, Suki D, Weinberg JS, Marmor E, Lang FF, Gershenson DM and Sawaya R: Brain metastases in patients with ovarian carcinoma: prognostic factors and outcome. J Neurooncol *66(3)*: 313-325, 2004.

8 Geisler JP and Geisler HE: Brain metastases in epithelial ovarian carcinoma. Gynecol Oncol 57(2):246-9,1995.

9 Kim TJ, Song S, Kim CK, Kim WY, Choi CH, Lee JH, Lee JW, Bae DS and Kim BG: Prognostic factors associated with brain metastases from epithelial ovarian carcinoma. Int J Gynecol Cancer *17(6)*: 1252-1257, 2007.

10 Lohr F, Pirzkall A, Hof H, Fleckenstein K and Debus J: Adjuvant treatment of brain metastases. Semin Surg Oncol *20(1)*: 50-56, 2001.

11 D'Andrea G, Roperto R, Dinia L, Caroli E, Salvati M and Ferrante L: Solitary cerebral metastases from ovarian epithelial carcinoma: 11 cases. Neurosurg Rev *28(2)*: 120-123, 2005.

12 Cormio G, Rossi C, Cazzolla A, Resta L, Loverro G, Greco P, Selvaggi L: Distant metastases in ovarian carcinoma. Int J Gynecol Cancer *13(2)*: 125-129, 2003.

13 Corn BW, Greven KM, Randall ME, Wolfson AH, Kim RY and Lanciano RM: The efficacy of cranial irradiation in ovarian cancer metastatic to the brain: analysis of 32 cases. Obstet Gynecol *86(6)*: 955-959, 1995.

14 Kolomainen DF, Larkin JMG, Badran M, A'Hern RP, King DM, Fisher C, Bridges JE, Blake PR, Barton DP, Shepherd JH, Kaye SB and Gore ME: Epithelial ovarian cancer metastasizing to the brain: a late manifestation of the disease with an increasing incidence. J Clin Oncol *20(4)*: 982-986, 2002.

15 Kumar L, Barge S, Mahapatra AK, Thulkar S, Rath GK, Kumar S, Mishra R, Dawar R, Singh R: Central nervous system metastases from primary epithelial ovarian cancer. Cancer Control *10(3)*: 244-253, 2003.

16 Pectasides D, Aravantinos G, Fountzilas G, Kalofonos C, Efstathiou E, Karina M, Pavlidis N, Farmakis D, Economopoulos T and Dimopoulos M: Brain metastases from epithelial ovarian cancer. The Hellenic Cooperative Oncology Group (HeCOG) experience and review of the literature. Anticancer Res *25(5)*: 3553-3558, 2005.

17 LeRoux PD, Berger MS, Elliott JP and Tamimi HK: Cerebral metastases from ovarian carcinoma. Cancer *67(8)*: 2194-2199, 1991.

18 Larson DM, Copeland LJ, Moser RP, Malone JM Jr, Gershenson DM and Wharton JT: Central nervous system metastases in epithelial ovarian carcinoma. Obstet Gynecol *68(6)*: 746-750, 1986.

19 Li ZT and Fu SL: Epithelial ovarian carcinoma metastatic to the brain: report on ten cases with review of literature. Zhonghua Fu Chan Ke Za Zhi *38(5)*: 287-289, 2003.

20 Bruzzone M, Campora E, Chiara S, Giudici S, Merlini L, Simoni C, Mammoliti S, Rubagotti A and Rosso R: Cerebral metastases secondary to ovarian cancer: still an unusual event. Gynecol Oncol *49(1)*: 37-40, 1993.

21 Kaminsky-Forrett MC, Weber B, Conroy T and Spaeth D: Brain metastases from epithelial ovarian carcinoma. Int J Gynecol Cancer *10(5)*: 366-371, 2000.

22 Ross WM, Carmichael JA and Shelley WE: Advanced carcinoma of the ovary with central nervous system relapse. Gynecol Oncol *30(3)*: 398-406, 1988.

23 Hardy JR and Harvey VJ: Cerebral metastases in patients with ovarian cancer treated with chemotherapy. Gynecol Oncol *33(3)*: 296-300, 1989.

24 Stein M, Steiner M, Klein B, Beck D, Atad J, Kuten A, Robinson E and Goldsher D: Involvement of the central nervous system by ovarian carcinoma. Cancer *58(9)*: 2066-2069, 1986.

25 Dauplat J, Nieberg RK and Hacker NF: Central nervous system metastases in epithelial ovarian carcinoma. Cancer *60(10)*: 2559-2562, 1987.

26 Tay SK and Rajesh H: Brain metastases from epithelial ovarian cancer. Int J Gynecol Cancer *15(5)*: 824-829, 2005.

27 Barker GH, Orledge J and Wiltshaw E: Involvement of the central nervous system in patients with ovarian carcinoma. Br J Obstet Gynaecol *88(7)*: 690-694, 1981.

28 Cooper KG, Kitchener HC and Parkin DE: Cerebral metastases from epithelial ovarian carcinoma treated with carboplatin. Gynecol Oncol *55(2)*: 318-323, 1994.

29 Budd GT, Webster KD, Reimer RR, Martimbeau P and Livingston RB: Treatment of advanced ovarian cancer with cisplatin, adriamycin, and cyclophosphamide: effect of treatment and incidence of intracranial metastases. J Surg Oncol *24(3)*: 192-195, 1983.

30 Pietzner K, El Khalfaoui K, Oskay-Özcelik G, Boehmer D, Lichtenegger W and Sehouli J: Brain metastases in ovarian cancer: Overview and optimal treatment. *28(5C)*: 3447, 2008.

31 Melichar B, Urminska H, Kohlova T, Nova M and Cesak T: Brain metastases of epithelial ovarian carcinoma responding to cisplatin and gemcitabine combination chemotherapy: a case report and review of the literature. Gynecol Oncol *94(2)*: 267-276, 2004.

32 Vlasveld LT, Beynen JH, Boogerd W, Ten Bokkel Huinink WW and Rodenhuis S: Complete remission of brain metastases of ovarian cancer following high-dose carboplatin: a case report and pharmacokinetic study. Cancer Chemother Pharmacol *25(5)*: 382-3, 1990.

33 Plaxe SC, Dottino PR, Goodman HM, Deligdisch L, Idelson M and Cohen CJ: Clinical features of advanced ovarian mixed mesodermal tumors and treatment with doxorubicin- and *cis*-platinum-based chemotherapy. Gynecol Oncol *37(2)*: 244-249, 1990.

34 Korfel A and Thiel E: Chemotherapy of brain metastases: Front Radiat Ther Oncol *33*: 343-348, 1999.

35 Oberhoff C, Kieback DG, Wurstlein R, Deertz H, Sehouli J, van Soest C, Hilfrich J, Mesrogli M, von Minckwitz G, Staab HJ and Schindler AE: Topotecan chemotherapy in patients with breast cancer and brain metastases: results of a pilot study: Onkologie *24(3)*: 256-260, 2001.

36 Gerstner ER and Fine RL: Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. J Clin Oncol *25(16)*: 2306-2312, 2007.

37 Lee YK, Park NH, Kim JW, Song YS, Kang SB and Lee HP: Gamma-knife radiosurgery as an optimal treatment modality for brain metastases from epithelial ovarian cancer. Gynecol Oncol *108(3)*: 505-509, 2008.

Received January 6, 2009
Revised March 5, 2009
Accepted April 2, 2009