

# Platinum Sensitivity as an Independent Prognostic Factor in Patients with Brain Metastases from Ovarian Carcinoma

Faisal Azam\*, Helen Wong, Khizar Hayat, Julie O'Hagan, Rosemary Lord, John Windara Green

Clatterbridge Centre for Oncology, Clatterbridge Road, Bebington, Wirral Merseyside CH63 4JY, United Kingdom

## Abstract

**Background:** The brain is a rare site of metastases from ovarian cancer. Limited data are available on prognostic factors, standard treatment, and survival. Knowledge of clinical prognostic factors would help the management of patients with brain metastases. The aim of this study is to evaluate the impact of clinical factors and treatment modalities on survival in patients with brain metastases from ovarian cancer.

**Methods:** We performed a retrospective analysis of an electronic database of patients with brain metastases from ovarian primary treated at Clatterbridge Centre for Oncology.

**Results:** A total of 20 patients with brain metastases from an ovarian primary were treated from April 2001-February 2011. Median age at occurrence of brain metastases was 55 years. The median time from primary diagnosis to occurrence of brain metastases was 23 months. Median overall survival from diagnosis of brain metastases was 9 months. Poor ECOG performance status, platinum resistance, and advanced FIGO staging were the most significant adverse variables identified. Median survival was 13 months for platinum sensitive patients and 6 months for platinum resistant patients.

**Conclusion:** Platinum sensitivity is an important prognostic factor in patients with brain metastases from an ovarian primary tumor. Multimodal therapy that consists of surgery, radiotherapy, and chemotherapy should be considered where feasible.

**Keywords:** Platinum sensitive, Ovarian cancer, Brain metastases, Chemotherapy, Radiotherapy, Surgery

### Corresponding Author:

Faisal Azam, MD  
Clatterbridge Centre for  
Oncology, Clatterbridge  
Road, Bebington, Wirral  
Merseyside CH63 4JY, UK  
Tel: +44-151-3341155  
Email: faisalazam@yahoo.com

## Introduction

Ovarian cancer is one of the leading causes of morbidity and mortality among gynecological malignancies.<sup>1</sup> The standard

treatment of epithelial ovarian cancer (EOC) involves primary optimal debulking surgery followed by platinum-based chemotherapy (CT). However, despite significant

improvements in surgery and CT it is still associated with a high rate of relapse and tumor-related death.<sup>2</sup> The abdomen is the usual site of relapse and metastases outside this area are rare.

Brain metastases from EOC are uncommon and usually a late manifestation of the disease in patients with prolonged survival after platinum-based CT. The incidence of brain metastases from EOC usually ranges from 1% to 2% although an incidence of more than 10% has also been reported.<sup>3-5</sup> As overall survival has increased with improvement in CT for the primary ovarian cancer, more patients will present with brain metastases. There is no standard treatment for these patients. Knowledge of prognostic and predictive markers is also limited but better understanding of clinical prognostic factors would help the management of these patients.<sup>6</sup> Platinum sensitivity is a well known prognostic factor with a positive impact on survival in ovarian cancer but its impact on survival after diagnosis of brain metastases is not well documented. This study evaluates the impact of clinical factors and treatment modalities on survival in patients with brain metastases from ovarian cancer.

### Patients and Methods

Patients with brain metastases from histologically confirmed EOC were identified by retrospective review of an electronic data base and clinical notes at Clatterbridge Centre for Oncology, a regional center serving a population of 2.1 million, from April 2001 to February 2011. Patients with histologically proven ovarian cancer and radiologically confirmed brain metastases were included. Patient demographics, clinical variables, treatment, and survival data were documented.

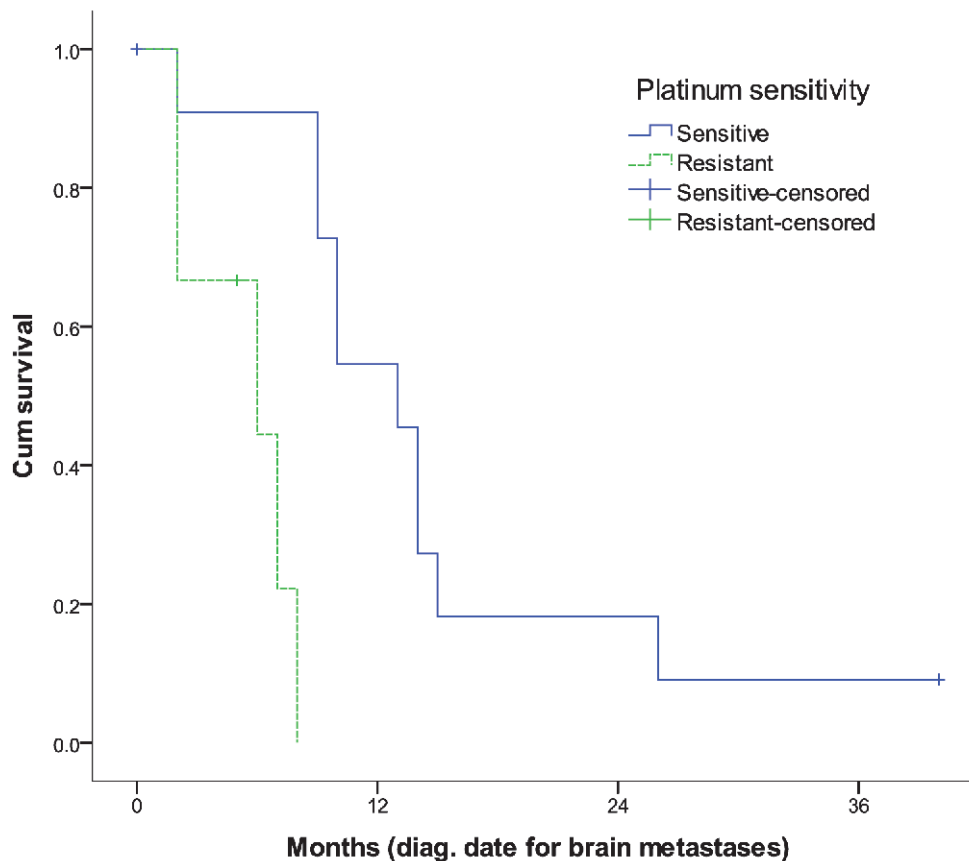
Variables included age at primary diagnosis, age at development of brain metastases, histology of ovarian cancer, FIGO stage at presentation of ovarian cancer, grade of ovarian cancer, ECOG performance status (PS) at the time of brain metastases, number of brain metastases, primary CT regimen, time to CNS relapse, and treatment of brain metastases. Survival was measured from

the diagnosis of primary tumor and from the diagnoses of brain metastases. The radiotherapy (RT) dose to the brain, the number of primary CT cycles and those for relapse has also been recorded. Platinum sensitivity was defined as relapse greater than six months after prior platinum CT.

Survival estimates were calculated using the Kaplan-Meier method and log-rank test. The Cox regression model was used to identify variables associated with survival. The adjusted hazard ratios and 95% confidence interval (95% CI) for variables were estimated. Statistical analysis was performed with SPSS version 19.

### Results

A total of 20 patients were identified in the period from April 2001 to February 2011. The median age at diagnosis of primary EOC was 52.5 years and 55 (range: 38-74) years at diagnosis of brain metastases. The median time from primary diagnosis to occurrence of brain metastases was 23 months (range: 1-208 months). The majority (n=15, 75%) had a good ECOG PS of 0 or 1. The most common histological type of ovarian tumor was serous with 18 (90%) patients followed by endometrioid in 1 (5%) patient, and mucinous in 1 (5%) patient. Most patients had FIGO stages III (n=9, 45%) and IV (n=6, 30%) disease at initial diagnosis of EOC and the most common histological grade was 3 (n=13, 65%). Multiple brain metastases were noted in 15 (75%) patients and were more common than single metastases seen in 5 (25%) patients. A total of 12 (60%) patients were platinum sensitive and 6 (30%) were resistant. Two patients did not receive any CT before the diagnosis of brain metastases. There were 16 (80%) patients with extracranial disease at the time of diagnosis of brain metastases (Table 1). Most (n=11, 55%) had multimodality treatment for brain metastases. Nine (45%) patients received monotherapy with whole brain RT (WBRT). All 20 patients had WBRT, either as a monotherapy or combined with other modality. Multimodality treatment included surgery and/or WBRT and/or CT. Four (20%) patients had CT



**Figure 1:** Overall survival from diagnosis of brain metastases

after WBRT and 4 (20%) had surgery followed by WBRT. In this study, 3 (15%) patients received all three treatment modalities (surgery, WBRT and CT; Table 2).

Of the 7 patients who received CT after the diagnosis of brain metastases, 6 received carboplatin. Four patients received single agent carboplatin, one patient had a combination of carboplatin with liposomal doxorubicin, one patient had a combination of carboplatin with paclitaxel, and one had single agent liposomal doxorubicin.

Doses of WBRT varied; the most common dose in 14 patients was 30 Gy in 10 fractions, 5 patients received 20 Gy in 5 fractions and one patient had 21 Gy in 7 fractions.

Median overall survival from diagnosis of brain metastases was 9 months (95% CI: 6.9-11.0 months). The median time from primary

diagnosis to occurrence of brain metastases was 23 months (range: 1-208 months). There were 17 out of 20 patients who died; 3 patients were still alive at 12, 16 and 39 months after diagnosis of brain metastases.

On univariate analysis, poor ECOG PS ( $P=0.029$ ) and platinum resistance ( $P=0.002$ ) were the most significant adverse variables that significantly impacted survival. Median survival was 13 months for platinum sensitive patients and 6 months for platinum resistant patients ( $P=0.001$ ; Figure 1). On multivariate analysis, platinum resistance and advanced FIGO stage were significant adverse prognostic factors.

All patients were treated with WBRT. Only 6 (30%) patients underwent surgical resection and 7 (35%) received CT. Patients treated with multimodal therapy had a median survival of 14 months ( $n=11$ ) compared to 8 months for RT only

**Table 1.** Patient and tumor characteristics.

<b>Total number</b>	20
Age (years) at brain metastases diagnosis	
Median	55
Range	38-74
<b>ECOG performance status (PS)</b>	<b>N (%)</b>
0	5 (25)
I	10 (50)
II	3 (15)
III	2 (10)
IV	0
<b>Histology (epithelial)</b>	
Serous	18 (90)
Endometrioid	1 (5)
Mucinous	1 (5)
<b>FIGO stage</b>	
I	4 (20)
II	1 (5)
III	9 (45)
IV	6 (30)
<b>Grade</b>	
I	0
II	5 (25)
III	13 (65)
Not specified	2 (10)
<b>Brain metastases</b>	
Single metastasis	5 (25)
Multiple metastases	15 (75)
<b>Platinum sensitivity</b>	
Sensitive	12 (60)
Resistant	6 (30)
<b>No prior chemotherapy (CT)</b>	2(10)

( $n=9$ ,  $P=0.011$ ). Median survival for patients treated with surgery and RT was 26 months, which was better than RT alone (median survival: 8 months), RT + CT (14 months) and surgery + RT+ CT (13 months; Table 2).

Clinical variables with no significant impact on survival were age, number of brain metastases, grade of the primary ovarian tumor, histological type, and doses of RT and CT regimens. There was no statistically significant difference in survival between patients aged less than 55 years or 55 years and older at the time of diagnosis of brain metastases.

## Discussion

Brain involvement in EOC is a rare occurrence

but its incidence has increased.<sup>7</sup> This increase in incidence could be related to improved control of the primary tumor with platinum-based CT.<sup>8-10</sup>

The median age of our patients was 55 years, which was consistent with that reported by other investigators.<sup>6, 11</sup> Performance status was the only prognostic factor consistently identified in all studies. Other identified prognostic factors that affected survival varied between studies.<sup>6, 12, 13</sup>

Most of our patients (75%) had stages III or IV disease at the time of initial diagnosis. This is in accordance with other studies in the medical literature, with the exception of Kolomainen et al., who reported that 33% of their patients with CNS involvement had stage I disease at the initial diagnosis of primary ovarian cancer.<sup>11,14</sup> In the current study, 25% of our patients had stages I or II disease. The most common histological type was serous and grade III was the most common differentiation for our patients, which was consistent with the experience of other investigators.<sup>8, 11</sup>

In our study patients who underwent multimodality treatment had a median survival of 14 months compared to 8 months for monotherapy (WBRT only) with a P-value of 0.011. This finding was in accordance with a study reported by Cohen et al.,<sup>3</sup> yet differed from a German study, in which Sehouli et al.<sup>6</sup> reported no significant survival benefit with a multimodal approach in 74 patients with brain metastases from ovarian cancer. Patients treated with the combination of surgery and WBRT had a better median survival (26 months) compared to WBRT alone or other treatment combinations in our study.

At the time of writing this paper, 3 of our patients were alive at 12, 16, and 39 months after their diagnosis of brain metastases. All 3 received multimodal therapy; 2 patients had surgery followed by WBRT while the third patient had WBRT followed by CT. One had lung metastases and other 2 had abdominal lymph node metastases before they developed brain metastases. All were platinum sensitive.

Although patients treated with the combination of surgery and WBRT in our study had a better survival outcome, this result should be interpreted

**Table 2.** Treatment modalities.

Treatment modalities	N (%)	Median survival (months)
Radiotherapy (RT) only	9 (45)	8
RT + chemotherapy (CT)	4(20)	14
Surgery + RT	4 (20)	26
Surgery + RT + CT	3 (15)	13

with caution as the sample size of our study was small. In many other studies, palliative RT alone was administered to 30%–50% of patients with multiple brain metastases.<sup>16-18</sup> Corn et al. and Melichar et al. reported a median survival of three to six months for patients treated with RT alone.<sup>17, 18</sup> No significant difference in response has been noted with the administration of 20 Gy radiation over one week compared with 50 Gy over four weeks according to Radiation Therapy Oncology Group (RTOG) studies. Thus a dose of 30 Gy in ten fractions over two weeks to the whole brain is a reasonable option.<sup>19-21</sup> Also no difference in survival was noted using hyperfractionated treatments compared with the standard 30 Gy in 10 fractions.<sup>22</sup>

Results from a prospective randomized study showed that patients with solitary brain metastases treated with surgical excision plus WBRT had a longer time to relapse, longer overall survival, and longer duration of functional independence when WBRT was added to surgery, compared with those patients treated with WBRT alone.<sup>23</sup> Pothuri et al.<sup>24</sup> at Memorial Sloan-Kettering Cancer Center and Cohen et al.<sup>3</sup> reported that the combination of surgery and WBRT was significantly better than surgery or WBRT alone. WBRT with stereotactic boost treatment was recommended in patients with less than three brain metastases by RTOG after a phase III randomized trial.<sup>25</sup>

Complete response of brain metastases after carboplatin has been reported in the literature.<sup>26, 27</sup> Melichar et al. reported response in a patient with brain metastases who was treated with cisplatin and gemcitabine.<sup>18</sup>

One of the interesting findings of our study was that platinum sensitivity was an independent prognostic factor. It had a significant positive

impact on survival regardless of the treatment modality used. In our study 12 (60%) patients were platinum sensitive. Median survival was 13 months for platinum sensitive patients and 6 months for platinum resistant patients ( $P \leq 0.001$ ; Figure 1). This finding was reported only once previously in the literature by Sehouli et al. who reported that 64.9% of their patients were platinum sensitive and had better survival (HR: 0.23, 95% CI: 0.12-0.46) compared to women with platinum resistant disease in the presence of brain metastases ( $P \leq 0.001$ ).<sup>6</sup>

In conclusion, CNS metastases in EOC are rare and most commonly a late manifestation of the disease. Patients with isolated solitary brain metastases are best treated by surgical resection followed by WBRT. Those with multiple brain metastases have poor prognoses but can still benefit from WBRT and systemic CT. Platinum sensitivity is an important prognostic factor in patients with brain metastases. Multimodal therapy with surgery, RT and CT should be considered when feasible.

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