Research Paper

Brain metastases in patients with EOC: Clinico-pathological and prognostic factors. A multicentric retrospective analysis from the MITO group (MITO 19)

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HIGHLIGHTS

• There is no consensus regarding the best management of patients with BM from EOC.
• BM is a rare manifestation of EOC, typically occurring in platinum sensitive women.
• Patients receiving multiple treatments for BM achieve a longer OS.
• BM from EOC is not a unique disease and tailored treatments should be proposed.

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ABSTRACT

Background. Brain metastases (BM) from epithelial ovarian cancer (EOC) are considered a rare and unfavourable event. There is no consensus regarding the best management of these patients.

Methods. A multicenter retrospective analysis of patients with BM from EOC treated between 1997 and 2014 in 18 institutions of the MITO (Multicenter Italian Trials in Ovarian cancer) group was conducted. Univariate and multivariate analysis were performed.

Results. A total of 174 women were identified as having BM from EOC. The median time interval between primary diagnosis of EOC and occurrence of BM was 26 months (range 2–129 months). The median overall survival from primary EOC diagnosis was 48 months (95% CI 39.5–56.4 months) and from diagnosis of BM was 12 months (95% CI 9.6–14.3 months). The majority of enrolled women (81.7%) were classified as sensitive to platinum-
based chemotherapy. Four variables were significantly associated with poor overall survival in multivariate analysis: multiple BM (HR: 1.86 [95% CI: 1.22–2.84]), presence of extracranial disease (HR: 1.77 [95% CI: 1.11–2.83]) age (HR: 1.74 [95% CI: 1.17–2.59]), and monotherapy (HR: 2.57 [95% CI: 1.64–3.86]). On the contrary, residual tumor at primary surgery, FIGO stage at primary diagnosis and platinum sensitivity were found to have no significant impact on survival from diagnosis of brain lesions.

Conclusions. Our results suggest that BM is a rare and late manifestation of EOC, with a 12-month life-span expectation. Multiple approach is a positive independent prognostic factor and should be proposed to carefully selected patients.

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56.4 months) and from diagnosis of BM was 12 months (95% CI 9.6–14.3 months).

Prognostic factors associated with shorter survival were the presence of extracranial disease at the time of brain relapse (11 vs 24 months, p = 0.003, Fig. 1), and multiple cranial lesions (10 vs 23 months, p = 0.0001, Fig. 2). Patients with platinum-sensitive relapses presented a longer survival (14 vs 6 months, p = 0.0001, Fig. 3) than women with platinum-resistant disease. Women who were treated with multimodality approaches achieved a median OS of 22 months from diagnosis of BM, compared with 5 months for those who received unimodal treatment (p = 0.0001; Fig. 4).

Among patients with a single intracranial lesion, without extracranial disease, 7 out of 30 (23.3%) received a single treatment whereas 23 (76.7%) received a combined approach; overall survival of patients receiving multimodal treatment was longer than OS of those treated with a single approach (46 vs. 12 months, log rank p = 0.084) (Table 4). Among 43 patients with single BM and extracranial disease, 9 (20.9%) received a single treatment whereas 31 (72.1%) received a combined approach; this latter group showed an overall survival of 27 months, compared with 8 months of the single approach group (log rank p = 0.01). Finally, the majority of patients who presented with multiple BM associated with extracranial disease were 26 months of OS, compared with 5 months OS of patients receiving single treatment (log rank p = 0.01).

Additionally, considering patients who had multiple intracranial lesions without extracranial disease, 12 out of 20 (60%) received a single treatment compared with 8 (40%) who received a combined approach; this group showed a longer survival of 27 months, compared with 8 months of the single approach group (log rank p = 0.01). Finally, the majority of patients who presented with multiple BM associated with extracranial disease received a multimodality approach (64.1%) and achieved a 9-month OS increase compared with those who received a single treatment (log rank p = 0.0001).

Among patients who received combination of surgical resection, radiotherapy and chemotherapy, 61% (25 patients) presented with single BM compared with 39% (16 patients) who had multiple BM; concomitant extracranial disease was found in 27 patients (66%); among this group of patients, median OS was 24 months.

Four variables were significantly associated with poor OS in multivariate analysis (Table 5): multiple BM [HR: 1.86 (95% CI: 1.22–2.84)], presence of extracranial disease [HR: 1.77 (95% CI: 1.11–2.83)] age [HR: 1.74 (95% CI: 1.17–2.59)], and monotherapy [HR: 2.57 (95% CI: 1.64–3.86)]. On the contrary, residual tumor at primary surgery, FIGO stage at primary diagnosis and platinum sensitivity were found to have no significant impact on survival from diagnosis of brain lesions.

4. Discussion

In this retrospective multicentre study we found that BM is a rare and late manifestation of EOC, typically occurring in platinum sensitive patients and presenting with multiple brain lesions, with a 12-month life-span expectation. We also found that younger patients, with single and isolated BM, and those who received multiple treatments for BM achieved a longer OS after BM diagnosis (Table 5).

During the last two decades, the survival of EOC patients has improved due to the improvement of surgical techniques and the availability of novel anticancer agents. Considerably more patients live long enough to be at an increased risk of developing brain metastases [6,7]. Data regarding this setting of patients are still scarce and not

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**Table 1**

Patients characteristics.

<table>
<thead>
<tr>
<th>Histology</th>
<th>N [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>135 (77.6)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>13 (7.5)</td>
</tr>
<tr>
<td>Clear cells</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>11 (6.3)</td>
</tr>
</tbody>
</table>

**Table 2**

Clinical characteristics of brain metastases (BM).

| No symptoms at diagnosis | 45 (25.9) |
| Presence of symptoms at diagnosis | 125 (71.8) |
| Missing | 4 (2.3) |

**Table 3**

Overview of treatments administered to patients with BM.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>38 (21.8)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>Radiotherapy + chemotherapy</td>
<td>55 (31.6)</td>
</tr>
<tr>
<td>Radiotherapy + surgery</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>Chemotherapy + surgery</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>Radiotherapy + chemotherapy + surgery</td>
<td>41 (23.7)</td>
</tr>
<tr>
<td>No treatment</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>Total</td>
<td>174 (100)</td>
</tr>
</tbody>
</table>
homogeneous. Furthermore, many of these patients are supposed to have a very limited life span following the diagnosis of BM. A clear understanding of predictors of survival can help physicians tailor treatment to the individual patient [15].

Our series represents the largest dataset reporting on clinicopathological presentations and prognostic factors of BM in EOC.

First of all, it should be noticed that almost 1 out of 4 patients who were diagnosed with BM did not complain of any neurological symptoms and were diagnosed during routine follow up (Table 2). It should also been underlined that the majority (64%) of asymptomatic patients have been diagnosed with BM since 2011, compared with 13 (36%) who have been diagnosed between 1997 and 2010. This reflects the widely

Fig. 1. Kaplan–Meier survival curves of OS after BM diagnosis in patients with BM alone vs. patients with BM in association with extracranial disease (24 vs 11 months, p = 0.003).

Fig. 2. Kaplan–Meier survival curves of OS after BM diagnosis in patients with single BM vs. patients with multiple BM (23 vs 10 months, p = 0.0001).

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different follow-up practice patterns across MITO centres and the increasing number of referral hospitals in which whole body radiological assessment is performed.

Furthermore, we found that approximately 70% of patients with BM had no lung or liver metastases at the time brain metastases appeared. There is a possibility that the lung or liver lesions may have been so small that even CT scan could not detect them. However, in view of the high incidence of no lung/liver metastases at the time BM appeared, there might exist an alternative route from the abdomen to the brain that could explain this occurrence, as initially proposed by Batson et al. [16], without subsequent confirmation. Therefore the question whether or not we should include brain imaging in our standard follow-up, still unsolved in the international guidelines [17], needs to be answered, particularly in the light of this evidence.

Results from the present study corroborate other previous evidences, according to which BM is more common in platinum-sensitive
patients [18]. Due to this exquisite longer platinum-sensitivity associated with BM, we can argue that a part of these patients with BM were carrying a BRCA germline mutation [19]. However, data on genetic assessment were not available in this collected series but it would be reasonable to investigate this potential correlation in further studies.

Sehouli et al. [18] found that platinum sensitivity had also a highly significant positive impact on survival, but this association is not supported by the results of our multivariate analysis. Indeed, we found that multiple BM or accompanied with extracranial disease occur more often in platinum resistant patients, than in the platinum sensitive counterpart.

In our study, the only factors correlating with better prognosis of EOC patients with BM were younger age, absence of extracranial disease, presence of single lesion and multimodality approach.

Previous studies have shown inconsistent results regarding the impact of extracranial disease on outcome. In fact, Cormio et al. [20], and Anupol et al. [21] suggested an association between the presence of systemic disease and shorter survival while other authors did not confirm this assumption [7,18]; this might be partly due to the small sample size of the above mentioned series. Similarly, there is no agreement on the association between single lesion and a better prognosis [5,18,22]; our findings strengthen this hypothesis and we report a 15-month OS improvement for those patients who only have intracranial single lesion, without extracranial disease (30 vs. 15 months, log rank p = 0.07). Obviously, it should be underlined that patients with a single intracranial lesion received a combined approach in >70% of cases, suggesting that physicians are more keen on “aggressive” treatments in this setting of patients.

Treatment options for BM, other than corticosteroids and antiepileptics, include systemic chemotherapy, radiotherapy (whole-brain irradiation therapy, stereotactic radiosurgery, including gamma-knife radiosurgery), and surgical resection [23-25]. Many authors suggested that a multimodality treatment is associated with a better outcome [26,27], and the results of our analysis seem to confirm this suggestion: >60% of our patients received multimodality treatment, which is a higher percentage compared with the majority of other experiences, and this might also explain the longer survival we recorded (median OS: 12 months), compared with that of other authors. On the other hand, it could also be argued that patients with better prognostic features and good performance status were more likely to receive multiple treatments and, reasonably, the enhanced survival has to be more related with the overall clinical conditions than with treatment choice. Regardless, it should be highlighted that in our analysis each subgroup of patients obtained an OS improvement when the multiple approach was preferred, irrespective of the presence of multiple BM and/or extracranial disease. Given the retrospective nature of our analysis we cannot draw any definitive conclusions about the optimal therapeutic management of BM patients; however it is reasonable to propose the multimodal approach in carefully selected patients who have a good performance status and may profit from effective tumor control in the brain.

### Table 4
Type of treatment and survival according to number of BM and presence of extracranial disease.

<table>
<thead>
<tr>
<th>N of pts</th>
<th>Single vs. combined treatment</th>
<th>Pts by treatment</th>
<th>Type of treatment</th>
<th>OS (months)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single intracranial lesion without extracranial disease</td>
<td>30</td>
<td>Single</td>
<td>7 (23.3%)</td>
<td>1 CT</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple</td>
<td>23 (76.7%)</td>
<td>3 RT</td>
<td>46</td>
</tr>
<tr>
<td>Single intracranial lesion with extracranial disease</td>
<td>43</td>
<td>Single</td>
<td>9 (20.9%)</td>
<td>1 CT</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple</td>
<td>31 (72.1%)</td>
<td>7 RT</td>
<td>26</td>
</tr>
<tr>
<td>Multiple intracranial lesions without extracranial disease</td>
<td>20</td>
<td>Single</td>
<td>12 (50%)</td>
<td>12 RT</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple</td>
<td>8 (40%)</td>
<td>1 RT-Surgery</td>
<td>27</td>
</tr>
<tr>
<td>Multiple intracranial lesions with extracranial disease</td>
<td>78</td>
<td>Single</td>
<td>20 (25.6%)</td>
<td>5 CT</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple</td>
<td>50 (64.1%)</td>
<td>15 RT</td>
<td>13</td>
</tr>
</tbody>
</table>

**Pt:** patients; **OS:** overall survival; **CT:** chemotherapy; **RT:** radiotherapy.

*a* Data about correlation between type of treatment received and number or site of disease were unavailable in 3 patients.

*b* 3 (7%) patients did not received any treatment.

*c* 8 (10.3%) patients did not received any treatment.

### Table 5
Univariate and multivariate analysis of the factors for poor survival in ovarian cancer patients with brain metastasis.

| Absence vs presence of residual tumor at primary surgery | HR (95% CI) | p value | 1.732 (1.217–2.467) | 0.002 | 1.74 (1.17–2.59) | 0.006 |
| Single vs multiple lesions | 1.050 (0.993–1.09) | 0.819 | 1.09 (0.69–1.72) | 0.952 |
| BM alone vs BM + extracranial disease | 2.149 (1.464–3.153) | 0.0001 | 1.86 (1.22–2.84) | 0.004 |
| Platinum-sensitive vs. platinum-resistant | 1.819 (1.209–2.737) | 0.004 | 1.77 (1.11–2.83) | 0.015 |
| Multiple treatment vs. single treatments | 2.083 (1.367–3.72) | 0.001 | 1.31 (0.80–2.13) | 0.27 |
| Multiple treatment vs. single treatments | 2.91 (1.38–4.28) | 0.0001 | 2.517 (1.64–3.86) | 0.0001 |
| Age < 57 years vs ≥ 57 years | 1.372 (0.603–3.120) | 0.451 | 0.82 (0.35–1.90) | 0.65 |

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The major limitation of this study is its retrospective nature; for this reason and due to the multicentric nature of the study and the long time frame of enrollment, we were unable to define the cumulative incidence of BM in our study population. Despite meticulous adjustment analysis, undetected bias could confound the results. Furthermore, because it was difficult to determine cause of death for many patients in this retrospective analysis, we could not determine BM-specific survival, which would be a relevant measure of outcome in this population. Moreover, we were unable to catch specific details on the received treatments such as the schedule and dose of chemotherapy and radiotherapy. Nevertheless, this is the largest series reported on this topic in EOC and, by identifying prognostic factors, it might support decision making in a clinical scenario where there was previously a lack of robust data and unanimous guidelines are certainly not yet in sight.

In conclusion, BM in EOC have traditionally been considered as a “fatal” event, with a rapid and incontrovertible decline in life expectancy. Our data suggest the routine introduction of brain imaging during EOC follow-up; this important issue deserves further and careful investigation. Furthermore, albeit deserving to be confirmed in prospective studies, our results suggest that BM from EOC are not a unique disease and patients who come across this occurrence should be carefully investigated to define the tumor’s spread and, consequently, they should receive a tailored treatment.

Conflict of interests
Domenica Lorusso has attended advisory boards for AstraZeneca and Roche.

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References