Prognostic role of early versus late onset of bone metastasis in patients with carcinoma of the ovary, peritoneum and fallopian tube

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Background: Bone metastases are a rare manifestation in the management of ovarian cancer and thought to be associated with a poor prognosis as sign of distant spread. Only few data exist on this rare condition. The present study aimed to more information on this very distinct patient collective.

Patients and methods: A retrospective chart review was carried out including all patients who had been treated from 1994 to 2009 for histologically confirmed ovarian, peritoneal and fallopian tube cancer. Overall, 1717 cases were detected and screened. Patients with bone metastasis were identified and analyzed regarding survival as well as various clinical variables.

Results: A total of 26 women who had been diagnosed with bone metastases ante mortem could be identified, resulting in an incidence of 1.50%. The majority of patients presented multiple bone lesions (80.8%) and bone spread was symptomatic in 62.5% of the cases. Mean overall survival from primary diagnosis of EOC was 50.5 months (range: 2.5–142.5 months). Median overall survival after diagnosis of bone metastases was 7.2 months. When divided into two subsets depending on timepoint diagnosis of bone metastases, there was a significant difference in overall survival. The mean overall survival from primary diagnosis of EOC in the early-onset group (n = 8), defined as occurence of bone manifestation within 12 months, was 11.2 months. The mean overall survival in the late-onset group (n = 15) was 78.4 months (P = 0.000001).

Conclusions: The time interval from diagnosis to appearance of bone metastases is a prognostic factor in ovarian cancer. While early onset bone spread has a strong negative prognostic impact, late-onset bone diagnosis of bone metastases hardly influences the prognosis at all. This finding should be considered in the management of patients with bone metastases from ovarian cancer.

Key words: bone metastases, ovarian cancer, prognostic factors

introduction

Bone metastases are a common pattern of metastatic spread in malignant tumors and become clinically apparent in 13%–33% of all carcinomas, with a detection rate of up to 90% at postmortem autopsy. However, bone manifestation is extremely rare in ovarian cancer patients. Even though epithelial ovarian cancer (EOC) is responsible for ~190 000 newly diagnosed cases and 114 000 annual deaths, making it the gynecological cancer with the highest mortality rate, the clinical incidence of bone metastases in ovarian carcinoma was reported to be as low as 1% [1–6]. Corresponding with other carcinomas the postmortem detection rate at autopsy was found to be much higher, with an incidence of ~10% [7, 8]. The metastatic pattern and symptoms found in patients with ovarian cancer are in line with findings in other tumor entities who frequently cause bone lesions. The most frequent metastatic sites are considered to be the vertebral column and sternum, followed by the ribs, pelvic and cranial bones and the most frequently reported symptom in previous publications was pain [1–6]. Despite the fact that information on this rare condition is mostly limited to case reports, bone metastasis from ovarian cancer is considered to be linked with a poor prognosis as a sign of hematogenous spread with a median survival of ~8 months from the timepoint of diagnosis [1–6]. Even though the occurrence of metastatic spread to the skeletal system poses a great challenge in the management of ovarian cancer and other carcinomas alike, very few clinical data exist on bone lesions from ovarian cancer, due to the rareness of this manifestation. Therefore, the present analysis was initiated to gain new information on this very special patient collective.
patients and methods
A retrospective chart review was carried out for all patients who had been treated at Charité–University Medicine of Berlin for histologically confirmed ovarian, peritoneal and fallopian tube cancer in the period from 1994 to 2009. The medical charts were systematically analyzed and demographic as well as various clinical parameters were extrapolated to a study dataset using Excel, 2003 (Microsoft, Redmond, WA). Documented demographic factors included age, stage, histological subtype and grading at primary diagnosis, while clinical characteristics contained number of bone metastases, presence of extraskeletal disease and ascites at time of diagnosis, outcome of primary surgery, serum values for calcium and alkaline phosphatase at time of primary diagnosis and occurrence of bone lesions, as well as symptoms and complications related to bone affection. Also the modality and type of treatment was documented (unimodal versus multimodal) and patients were classified as platinum sensitive or platinum resistant (relapse >6 months versus relapse <6 months after prior platinum therapy, respectively). Survival from the timepoints of primary diagnosis as well as manifestation of bone metastases was evaluated.

statistical analysis
All results are presented as frequency and rate for categorical variables or median and range for continuous variables. Survival curves were estimated according to the Kaplan–Meier method. Log-rank tests were used for univariate statistical comparisons. The relative importance of variables as independent predictors of overall survival was analyzed with the multivariate Cox proportional hazard regression. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for prognostic factors were estimated. All data were analyzed using SPSS version 18.0.0, 2009 (SPSS, Inc., Chicago, IL), and a P value of <0.05 was considered statistically significant.

results
patients characteristics and clinical parameters
Of 1717 patients with histologically confirmed EOC, peritoneal and fallopian tube cancer that had been screened, a total of 26 patients could be identified with bone metastases that had been apparent antemortem, resulting in an incidence of 1.50%. At the stage III, which was found in 15 (57.7%) patients (Table 1). Of 1717 patients with histologically confirmed EOC, peritoneal and fallopian tube cancer was 73.1%, 19.2% of 15 (57.7%) was found to be postmenopausal. The distribution of EOC, peritoneal and fallopian tube cancer in the period from 1994 to 2009. The medical charts were systematically analyzed and demographic as well as various clinical parameters were extrapolated to a study dataset using Excel, 2003 (Microsoft, Redmond, WA). Documented demographic factors included age, stage, histological subtype and grading at primary diagnosis, while clinical characteristics contained number of bone metastases, presence of extraskeletal disease and ascites at time of diagnosis, outcome of primary surgery, serum values for calcium and alkaline phosphatase at time of primary diagnosis and occurrence of bone lesions, as well as symptoms and complications related to bone affection. Also the modality and type of treatment was documented (unimodal versus multimodal) and patients were classified as platinum sensitive or platinum resistant (relapse >6 months versus relapse <6 months after prior platinum therapy, respectively). Survival from the timepoints of primary diagnosis as well as manifestation of bone metastases was evaluated.

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results
patients characteristics and clinical parameters
Of 1717 patients with histologically confirmed EOC, peritoneal and fallopian tube cancer that had been screened, a total of 26 patients could be identified with bone metastases that had been apparent antemortem, resulting in an incidence of 1.50%. At the end of study, 3 of the 26 patients were still alive and were therefore excluded from survival analysis. Median age at primary diagnosis was 54.0 years (range 19–63 years) (Table 1). A total of 11 (42.3%) patients was premenopausal, while a total of 15 (57.7%) was found to be postmenopausal. The distribution of EOC, peritoneal and fallopian tube cancer was 73.1%, 19.2% and 7.7%, respectively. The most frequent histological subtype was serous papillary with a total of 14 (53.8%) patients and the most frequently found FIGO stage at primary diagnosis was stage III, which was found in 15 (57.7%) patients (Table 1). At time of primary diagnosis, ascites was present in 38.5% of the patients and bone metastases were found in three patients. The majority of patients (21/80.8%) presented with multiple metastases at diagnosis of bone involvement, while only five patients (19.2%) had single lesions. The most frequent localization of bone metastases was found to be the spinal collum (n: 40; 56.3%) with with a distribution of 17 metastases in the lumbal (23.9%), 16 in the thoracic (22.5%) and 7 (9.9%) in the cervical section, respectively. This was followed by the pelvic bone (n: 16; 22.5%), ribs (n: 12; 17.0%), bones of the extremities (n: 4; 5.6%) and the skull (n: 2; 2.8%).

Sufficient documentation for the evaluation of symptoms of bone affection was available in 24 women. In these women, metastasis of the skeletal system remained asymptomatic in only seven cases (29.2%), while the main documented symptoms were pain, impaired mobility and neurologic symptoms which were found in 16 (66.7%), 9 (37.5%) and 4 (16.7%), respectively. Pathologic fractures were reported in 8 (33%) cases.

laboratory results
Calcium was normal in all patients with available documentation at primary diagnosis of bone metastases (n = 19) and on last available entry (n = 22). Alkaline phosphatase at time of primary diagnosis of ossary lesions was available in 19 patients. Elevated levels were found in 10 patients (mean value: 162 U/l) while 9 patients had normal levels (mean value: 83.2 U/l).

imaging studies and biopsies
Imaging studies that were conducted for detection of bone lesions included conventional X-ray (16 of 24), computed tomography (24 of 26), magnetic resonance imaging (16 of 26) and bone scintigraphy (20 of 26). The method with the highest detection rate was CT, followed by scintigraphy (supplementary Figure S1, available at Annals of Oncology online). Biopsy confirming histologic diagnosis of malignant bone lesion was carried out in four patients, all other patients were included in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Primary cancer</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>19 (73.1)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Histology serous</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Median age: histology serous</td>
<td>54</td>
</tr>
<tr>
<td>Number of early/late onset: serous</td>
<td>4/10</td>
</tr>
<tr>
<td>Histology adeno</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Median age: histology: adeno</td>
<td>41</td>
</tr>
<tr>
<td>Number of early/late onset: serous</td>
<td>4/2</td>
</tr>
<tr>
<td>Grading I/II</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>Grading III</td>
<td>12 (46.2)</td>
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<tr>
<td>Grading n.a.</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>FIGO stage I/II</td>
<td>4 (15.3)</td>
</tr>
<tr>
<td>FIGO stage III/IV</td>
<td>22 (84.7)</td>
</tr>
<tr>
<td>Single bone lesion</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Multiple bone lesions</td>
<td>21 (80.8)</td>
</tr>
<tr>
<td>Symptomatic bone lesions</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Asymptomatic bone lesions</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Symptoms n.a.</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Family history of EOC or breast cancer</td>
<td>4 (15.4)</td>
</tr>
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the analysis when radiologic assessment left no doubt that the bone lesion is of malignant origin.

**treatment modalities and survival**

Primary debulking surgery was carried out in 25 of the 26 patients and macroscopically tumor free resection could be achieved in 44%. Platinum-based first-line chemotherapy was applied 24 patients, 19 of those in combination with paclitaxel.

Median overall survival from diagnosis of EOC was 50.5 months (range: 2.5–142.5 months). Three patients (11.5%) were still alive at the time of the analysis. The median overall survival after diagnosis of bone metastases was 7.2 months (Figure 1). When divided into two subsets depending on timepoint diagnosis of bone metastases, there was a significant difference in overall survival. The mean overall survival from primary diagnosis of EOC in the early-onset group ($n = 8$), defined as occurrence of bone manifestation within 12 months, was 11.2 months. The mean overall survival in the late-onset group ($n = 15$) was 78.4 months (supplementary Figure S2, available at Annals of Oncology online). The difference was rated as highly significant in statistical analysis ($P = 0.000001$). The mean overall survival from diagnosis of bone metastases was 7.2 months in the early-onset group and 17.3 months in the late-onset group, respectively ($P = 0.072$). The patient characteristics of the early- and late-onset group are demonstrated in supplementary Table SII, available at Annals of Oncology online.

The worst prognosis was found for a group of four patients who presented with bone metastases at timepoint of primary diagnosis of EOC. These patients were all rated as platinum resistant after first-line therapy and had a mean overall survival of 3.3 months. High-grade carcinomas were found to develop bone metastases more often than low and intermediate grade carcinomas put together (10 versus 9). Grading did not have a significant impact on survival, with a mean overall survival of 62.5 months for low- and intermediate grade carcinomas and 42.5 months for high-grade carcinomas ($P = 0.354$). The mean overall survival for patients that were labeled platinum sensitive at timepoint of diagnosis of bone metastases was 11.8 months, while platinum resistant patients survived for a mean duration of 14.7 months ($P = 0.017$; Figure 2). A different situation was found at timepoint of first recurrence/progression: patients that were labeled platinum sensitive at this point survived longer with a mean survival of 70.0 months, compared with 35.5 months for platinum-resistant patients ($P = 0.059$).

The mean overall survival for patients who achieved macroscopically tumour-free resection at primary debulking surgery was 65.4 months, compared with 57.3 months for patients with suboptimal debulking. Patients with a single-bone lesion had a mean overall survival of 91.0 months, while multiple lesions were associated with a mean overall survival of only 47.5 months. However, this difference did not reach statistical significance ($P = 0.064$). Apart from the number of metastases, no significant prognostic value was also noted for the factors grading, age and pre- or postmenopausal status.

Response of the bone metastases to systemic as well as local therapy such as radiation was rated as stable in 25%, but progression of the bone lesions under therapy was noted in 75% of the cases, respectively. The fast majority ($n = 23/88.5$%) of patients was treated with bisphosphonates (zoledronat 19/23: 4 mg/kg bw q4w i.v.; pamidronat 4/23: 90 mg/kg bw q4w i.v.). Only three patients remained without bisphosphonates (patients’ wish 1 of 3; no reason documented 2 of 3) and two of these three patients presented with pathological fractures in the consecutive course of disease. The frequency of pathological fractures in patients with bisphosphate treatment was 26.1% ($n = 6$). Radiation of ossary lesions was carried out in 8 cases (dose of radiation 33 gray: 5 of 8; no dose documented: 3 of 8) due to pain ($n = 6$) or risk for fracture ($n = 2$). Pain reduction was documented in two cases, while one patient remained at a stable pain level after radiation and no documentation was found in the rest of the cases. Orthopedic surgery due to pathologic fractures was carried out in six cases. All patients received analgetics in the course of the disease. Analgetics of WHO-pain ladder step III were documented in 53.8% ($n = 17$).
discussion

The present study represents, to the best of our knowledge, the largest collective of patients with bone metastases from ovarian cancer that has been analyzed ante mortem up to this point. The largest previously reported collective was investigated by Clain et al. in 1965 with 11 cases included in their analysis, followed by 4 published by Dauplat et al. in 1987, 3 reported by Kumar et al. in 1992 and 2 published by Abdul-Karim et al. in 1990 and Cormio et al. in 2003, respectively [4, 5, 9–11]. Other experiences published to date are limited to case reports. The incidence of bone metastases in our collective was 1.5%, representing results of previous reports of ante mortem studies. However, the observed incidence has to be interpreted as a strong underestimate of the real figure. This is due to the fact that screening for bone metastases is not part of the routine follow-up, and the present study was conducted as an ante mortem clinical analysis rather than an autopsy study. Postmortem evaluation report an incidence of bone metastases of around 10%, suggesting that every 10th patient with ovarian cancer suffers from bone metastasis [8].

According to the findings in our study, bone metastases from ovarian cancer are not likely to respond to systemic chemotherapy, with 75% of the lesions progressing under therapy. However, patients will benefit greatly from stabilizing procedures such as radiation or orthopedic surgery. Also the therapy with oral bisphosphonates remains indispensable in order to stabilize lesions at risk for fracture and might even have a positive impact on overall survival, according to data recently published on patients with bone lesions from breast cancer [12, 13]. Even though, the incidence of bone lesions might be too low to incorporate bone imaging studies into the clinical routine of patients with ovarian cancer, the presence of treatment options and the suspected high rate of undiagnosed lesions highlight the need for early diagnostic procedures for patients under suspicion of symptomatic bone manifestation. Therefore, clinicians should be aware of the possibility of bone lesions in patients with typical symptoms and should consider imaging, with CT-scan as the imaging study of choice.

A surprising finding of this study was the fact that the timepoint of bone manifestation had an influence on the overall survival. As suspected, the occurrence of bone manifestation all in all was obviously associated with a negative impact on survival with a very short median overall survival of 7.2 months after diagnosis. This was anticipated with bone metastases being a sign of distant spread. Interestingly, this negative impact was most apparent when bone manifestation was diagnosed at an early timepoint or with primary diagnosis. Late onset of bone metastatization or the late diagnosis of bone spread, respectively, did however hardly affect the overall prognosis of these patients. This finding might be explained by a pre-selection of patients. It could be hypothesised that bone metastatization at an early timepoint impacts the whole collective with its detrimental influence on survival, while metastatization at a later timepoint occurs in individuals that have survived up to this point due to beneficial basic characteristics. This implies, that other individuals of the same collective have already died at this point. In detail, this could mean that late onset bone spread affects only the fit survivors of the whole collective that are not influenced by the detrimental impact of bone manifestation as strongly as nonselected individuals of the whole collective. Another explanation might be two different tumor behaviors that might both cause bone metastases. The early-onset type might be characterized as an aggressive type that causes early bone manifestation as sign of early spread and aggressiveness and is associated with resistance to standard chemotherapy and therefore a very poor prognosis. In the late-onset type on the other hand, bone metastatization might very well be an expression of the relatively low malignant potential, with tumor cells only nesting in the beneficial environment of the bone matrix that promotes tumor cell attachment and growth due to, e.g. slow blood flow and matrix-based growth factors [14–16].

This hypothesis might be supported by the very long overall survival from primary diagnosis in the late-onset group of our study, which significantly exceeds the life expectancy of ordinary patient with recurrent ovarian cancer.

Another factor that had prognostic significance was platinum sensitivity at timepoint of first diagnosis. This was anticipated since response to platinum-based chemotherapy is a well-known prognostic factor [17]. However, platinum sensitivity lost its prognostic significance after the occurrence of bone metastases, meaning that once patients had developed ossary spread, those patients who were labeled platinum sensitive at this point, had no survival benefit when compared with platinum-resistant patients. This might be explained by the fact, that after the occurrence of bone manifestation as a sign of end stage disease, the remaining survival time is so limited, that platinum sensitivity is not able to pose a beneficial impact. In contrary to our findings in patients with bone metastases, platinum sensitivity was able to translate its beneficial prognostic value into the similarly poor collective of patients with brain metastases from ovarian cancer in an analysis previously reported by our working group [17]. In this study including 74 patients with cerebral lesions, the overall prognosis after diagnosis of distant spread was equivalently poor, but in this population, platinum sensitivity was able to uphold its status as a positive prognostic factor [17]. Why these findings do not correlate remains unclear up to this point. On one hand, analyses with limited patient numbers due to the rareness of the researched condition remain under danger for selection bias; on the other hand, the different findings in these two collectives might be due to a different biological behavior of brain and bone metastases, respectively.

One hint to a different biological behavior is the fact that the overall prognosis of brain compared with bone metastases observed in both literature and clinical experience differs considerably, while brain metastasis is linked to a poor prognosis with a median survival of around 6 months widely independent from the primary tumor entity, the prognosis of bone manifestation does vary significantly depending on the type of primary. On one end of the spectrum prostate cancer is associated with a median overall survival of up 34.9 months, while bone metastases from hepatocellular carcinoma yield a grim prognosis with a median survival of only 4.6 months [18].

These observations might support the argument of a different clinical behavior leading to the different impact of platinum sensitivity on overall survival in patients with brain spread.
compared with bone metastasis. But as the overall survival from
timepoint of diagnosis of the metastasis was quite similar in
both studies with 7.2 and 7.4 months, this argument alone is not
sufficient to explain the differences found in both analyses.

**Conclusion**

The most important finding of this study was the different
prognostic impact of early-onset bone metastasation in
comparison to late-onset bone manifestation. The fact that late-
onset bone spread hardly influences the overall prognosis
should be remembered by the clinician, before limiting the
patient to a purely symptomatic therapy regime due to the
finding of bone metastases only.

**Disclosure**

The authors have declared no conflicts of interest.

**References**

1. Bruferman G, Krasnokuki D, Biran S. Metastatic bone involvement in gynecological
2. Chen YL, Hsiao SM, Lin MC et al. Bone metastasis as the initial presentation in
one case of ovarian cancer with two components of endometrioid adenocarcinoma
ovarian carcinoma: an analysis of 20 cases. Int J Gynecol Cancer 2009; 19:
611–614.
6. Dinh TV, Liebowitz BL, Hannigan EV et al. Bone metastasis in epithelial ovarian
7. Guth U, Huang DJ, Bauer G, Steiger M et al. Metastatic patterns at autopsy in
8. Reed E, Zerbe CS, Brawley OW et al. Analysis of autopsy evaluations of ovarian
11. Abdull Karim FW, Kida M, Wenz WB et al. Bone metastasis from gynecologic
12. Gavelz-Munoz E, Rodriguez-Lescure A. The role of bisphosphonates of adjuvant
13. Coleman RE. Adjuvant bisphosphonates in breast cancer: are we witnessing
the emergence of a new therapeutic strategy? Eur J Cancer 2009; 45:
1909–1915.
14. Havens AM, Jung Y, Sun YX et al. The role of sirolimus CD164 (MGC-24v or
15. Ribotti D, Mangialardi G, Vacca A, Paget and the ‘seed and soil’ theory of
17. Sehouli J, Pietzner K, Harter P et al. Prognostic role of platinum sensitivity in
patients with brain metastases from ovarian cancer: results of a German
18. Liu NN, Shun DL, Chen XQ et al. [Clinical analysis of 355 patients with bone
metastasis of malignant tumors.]. Zhonghua Zhong Liu Za Zhi 2010; 32:
203–207.

**Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data**

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**Background:** The majority of women with ovarian cancer develop recurrent disease. For patients with a platinum-free
interval of >6 months, platinum-based chemotherapy is a treatment of choice. The benefit of a platinum-based
combination chemotherapy in randomized trials varies, and a meta-analysis was carried out to gain more secure
information on the size of the benefit of this treatment.

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