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ORIGINAL ARTICLE

Prognostic factors in endometrial cancer patients with bone metastasis

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ABSTRACT

Objectives: This study aims to examine the pattern and prognosis of osseous involvement and the role of orthopedic surgery in patients with endometrial cancer (EC) and to evaluate the quality of life, local tumor control, and survival of patients.

Patients and methods: Between January 2011 and December 2018, a total of 14 patients (median age: 60.5 years; range, 55 to 73 years) who were surgically treated for osseous metastasis of EC and followed for minimum 12 months were retrospectively analyzed. All patients were evaluated for their primary malignancy, characteristics of bone metastasis, and type of treatment related to musculoskeletal involvement. For evaluating the functional outcomes, the Visual Analog Scale (VAS) for pain and Eastern Cooperative Oncology Group (ECOG) performance status scale were used in the pre- and postoperative period.

Results: The median follow-up was 34.5 (range, 9 to 89) months. All patients had advanced-stage disease (FIGO Stage III-IV). Four patients had solitary and 10 patients had multiple bone metastases. The mean VAS score and ECOG performance status grades improved ($p<0.001$ and $p<0.05$, respectively). The median survival after detection of bone metastasis was 61 (range, 41 to 82) months.

Conclusion: Endometrial cancer patients with musculoskeletal pain should be investigated for the possibility of bone metastasis to tailor a prompt treatment and to achieve a better prognosis. Appropriate surgical treatment of bone metastasis may improve both pain and performance status in carefully selected patients.

Keywords: Bone metastasis, endometrial cancer, prognosis, surgical treatment, survival.

Endometrial cancer (EC) is the most common gynecologic cancer and has an increased incidence worldwide.[1-3] Although early-stage EC is known to have a very good prognosis with adequate treatment, one-third of these patients experience distant metastasis.[4] Endometrial cancer-related deaths are mostly due to distant metastases reducing overall survival.[5]

Bone metastases (BMs) in EC have been rarely reported and seen in only 0.8% of the patients.[6-9] The incidence has increased due to prolonged disease control and the use of improved radiological studies with ease. Most patients are diagnosed with BM in the recurrent setting and have extraosseous dissemination with multiple sites of BM.[10] This advanced stage usually results in poor survival in women with the metastatic disease, if theinitial diagnosis or relapse was considered incurable with traditional treatment modalities.[11]

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While managing EC patients, the presence of an oligometastatic state is not commonly recognized. It is usually defined as a state of controlled or resected primary site with a few metastases (1-3 or 1-5) that has proven.[12] Solitary or oligometastasis of the bone should not be evaluated as the same with multiple metastases. There is a number of patients who develop isolated metastases in specific anatomic sites and have long-term survival after appropriately targeted

treatment. A radical treatment rather than palliation of pain and preventing pathological fractures is needed in these patients. In particular, when the primary lesion is under control, this approach may lead to a long-term survival that has been shown in small series.[13]

The pattern of BM of EC is not largely described in the literature in this specific background. It is essential to understand metastasis patterns to gain a better prognosis with the proper patient management. When a distant metastasis to the bone is detected for this rare clinical entity, we believe that all patients do not have the same prognosis for different metastasis locations, the number of metastasis, or types of orthopedic surgery. In the present study, we aimed to investigate the pattern and prognosis of osseous involvement in patients with EC to better understand the role of orthopedic intervention in this patient population.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ankara University Faculty of Medicine, Department of Orthopedics and Traumatology between January 2011 and December 2018. Patients who underwent orthopedic surgeries for metastatic gynecological cancers in our center were reviewed. A total of 14 patients (median age: 60.5 years; range, 55 to 73 years) with BM due to EC and with a minimum of 12 months of follow-up were included in this study. The confirmation of EC metastasis was performed with imaging studies followed by bone biopsy and confirmed with a review of the pathology database for all patients after orthopedic surgery. We documented the International Federation of Gynecology and Obstetrics (FIGO) stage and grade which were recorded after the diagnosis of EC in patients. The FIGO stage is a surgical staging system for EC that is commonly used to state the disease stage without uncertainty among clinicians and to predict patients' outcomes and prognosis.[14] Tumor grade, also called the FIGO grade, is defined by the degree of glandular differentiation in a 3-tiered grading system; i.e., Grade 1, 2, and 3.[15]

After the medical records were systematically reviewed, patients with missing clinical data (n=3) and follow-up for less than one year were excluded from the study. Data including patient characteristics and primary tumor features such as the FIGO stage and grade, type of received treatment, and visceral organ metastasis were recorded. There were three types of treatment modalities: chemotherapy, radiation therapy, and surgery defined as "Yes" or "No". Clinical presentation and characteristics of musculoskeletal involvement, chosen orthopedic surgery modality, and follow-up data were collected. The patients' functional outcomes were evaluated with the Visual Analog Scale (VAS) for pain and the Eastern Cooperative Oncology Group (ECOG) performance status scale for level of functioning.[16,17] All measurements were noted for pre- and postoperative three months. The ECOG performance status scale, which is a tool for physicians to follow changes during or after treatment, represents the patient's capacity for daily living activities and self-care. This scale has scores ranging from 0 to 5, where 0 represents fully active, 4 indicates the completely disabled meaning limited to a chair or bed, and 5 indicates death. We only emphasized the results of the nearest preoperative and three-month-after assessments to avoid the effect of cancer recurrence on patient outcomes.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The paired t-test was used for comparison of parametric variables. The Kaplan-Meier method was used to estimate survival curves. A p value of <0.05 was considered statistically significant.

RESULTS

The histological diagnosis of EC for all patients was an endometrioid carcinoma. Patients' demographics and characteristics of primary tumors, BM, and associated clinical data are summarized in Table I.

The median follow-up was 34.5 (range, 9 to 89) months. At the initial diagnosis, all patients had advanced-stage disease (FIGO Stage III-IV). Thirteen patients (92.9%) received gynecological treatment initially and only one patient (7.1%) with an advanced clinical stage (FIGO Stage IVA) did not receive surgical treatment as the first-line treatment for EC. In the majority of the patients (72%), FIGO grades were poorly differentiated (Grade 3), and only 28% of the patients had Grade 1 disease. No distant metastasis, except for bone, was identified in four (28.6%) patients.

Bone metastasis was detected at a median of 34.4 (range, 0 to 96) months after the initial diagnosis of EC. Two (14%) patients had bone pain located at the site of BM which was present at the time of the initial diagnosis.

TABLE I
Demographic, clinical, and operative data of patients

Patient	Age (year)	BMI	FIGO stage	Grade	Treatment for primary tumor	Visceral organ metastasis	Bone metastasis			Orthopedic surgery			Patient-reported outcomes		Follow-up	
							Number	Site	Interval	Indication	Type	Additional therapy after surgery	VAS (Pre-/post-operative)	ECOG (Pre-/post-operative	Follow-up from orthopedic surgery (month)	Status
1	61	>30	IIIC2	3	Surg+chemo	-	Single	Ilium	At diagnosis	IP	Resection	RT	8/3	3/1	40	NED
2	60	>30	IIIC2	1	Surg+chemo	-	Single	Femur	96	PF	Resection arthroplasty	RT	7/3	2/3	74	NED
3	55	>30	IIIC	3	Surg	Lung	Single	Sacrum	3	IP	Resection	RT	6/2	2/1	54	NED
4	73	>30	IIIC1	3	Surg+chemo+RT	Lung	Single	Pubic bone	48	IP	Resection	RT	7/3	2/1	60	NED
5	56	>30	IIIC2	1	Surg	Lung	Multiple	Femur*/vertebrae	74	PF	Curettage+IMN with cement	RT	9/2	4/2	89	DOD
6	56	>30	IIIC	1	Surg+chemo	-	Single	Fibula	75	IP	Resection	RT	8/3	2/1	84	NED
7	60	28	IIIC	1	Surg+chemo	-	Single	Acetabulum	40	IP	Resection arthroplasty	RT	9/3	3/1	14	AWD
8	65	26	IIIC2	3	Surg+chemo	Lung	Single	Femur	12	IP	Resection arthroplasty	-	8/2	3/2	29	DOD
9	66	>35	IVA	3	Chemo+RT+TMX	Liver/lung/LN	Multiple	Femur*/tibia/ cranium	48	PF	Resection arthroplasty	-	9/4	2/3	15	DOD
10	55	24,2	IVA	3	Surg	Liver/LN	Single	Sacrum	At diagnosis	IP	Curettage	Chemo	8/2	1/2	26	AWD
11	61	>30	IIIC	3	Surg+chemo	Lung/adrenal gland	Single	Vertebrae	20	IP	Curettage	RT	8/3	1/1	21	DOD
12	68	17,2	IIIC1	3	Surg+chemo	Liver	Multiple	Vertebrae*/ sacrum/ilium/ ischium/pubic bone	9	PF	Curettage+spinal instrumentation	RT	9/3	4/2	52	AWD
13	63	27	IIIC2	3	Surg+chemo+RT	LN	Multiple	Femur*/tibia/ cranium/ mandible/maxilla	37	PF	Resection arthroplasty	RT	9/3	3/2	9	DOD
14	57	>30	IIIB	3	Surg+chemo	Liver	Single	Humerus	20	IP	Resection arthroplasty	-	8/3	2/1	16	DOD

Interval: Time to bone metastasis after diagnosis of EC; BMI: Body mass index; FIGO: International Federation of Gynecology and Obstetrics; VAS: Visual analogue scale; ECOG: Eastern Cooperative Oncology Group; Surg: Surgery; Chemo: Chemotherapy; IP: Intractable pain; RT: Radiotherapy; NED: No evidence of disease; IMN: Intramedullary nailing; AWD: Alive with disease; PF: Pathological fracture; DOD: Died of disease; TMX: Tamoxifen; LN: Lymph node; * Indicates the operation site.

Ten (71%) patients developed BM as their first recurrence, while two (14%) patients developed BM as a later recurrence. In these 12 patients, the overall median time from the initial diagnosis of EC to BM was 38.5 (range, 3 to 96) months. All patients had pain complaints located in the BM sites that was later confirmed.

All patients were treated for BM. Intractable/refractory pain in nine patients (64%) and pathological fracture in five (36%) patients were the indications for orthopedic surgery. Most patients were treated with a combination of therapies, while there was no standard protocol. Wide resection of the bone lesion with or without reconstruction was done in 10 (71.4%) patients and intralesional resection in four (28.6%) patients could be achieved. Ten (71.4%) patients received radiation therapy after orthopedic surgery and one (7.1%) patient received chemotherapy after orthopedic surgery. Hormonal therapy was given to one (7.1%) patient combined with the other treatments.

Four (28.6%) patients had solitary BM and no other distant metastasis was detected. One of these patients (Patient No. 1) was diagnosed with EC and simultaneously detected BM on the iliac bone. The other three patients were diagnosed with EC by solitary bone lesions. Ten (71.4%) patients had other distant metastases in addition to bone including lymph nodes, lung, liver, and adrenal gland.

The median time from the diagnosis of BM to death in the group who had multiple sites of metastasis along with bone was 52 (range, 27 to 77) months. However, no statistical comparison could be performed, as the patients who had isolated BM were all alive and sample size was limited.

The overall median survival for EC patients in our study was 163 (range, 46 to 280) months (Figure 1). The median survival for patients with BM at the time of initial diagnosis and patients had BM at the time of recurrence could not be compared due to the limited number of patients. The patients who had BM at the initial diagnosis were still alive: alive with disease (n=1) and with no sign (n=1).

Six (42.9%) patients died from primary disease, five (35.7%) patients were alive with no sign of disease recurrence, and three (21.4%) patients were alive without remission. New BMs were detected in one patient (Patient No. 12) during follow-up and no other orthopedic surgery was performed simultaneously. Although resection arthroplasty was performed for solitary osseous metastasis to acetabulum in Patient No. 7, it was evaluated as alive with disease due to a short period of follow-up (i.e., 14 months). One lesion in the liver was diagnosed as a first recurrence during follow-up in Patient No. 10 and non-surgical treatment was given.

The median survival after detection of BM was 61 (range, 41 to 82) months (Figure 2).

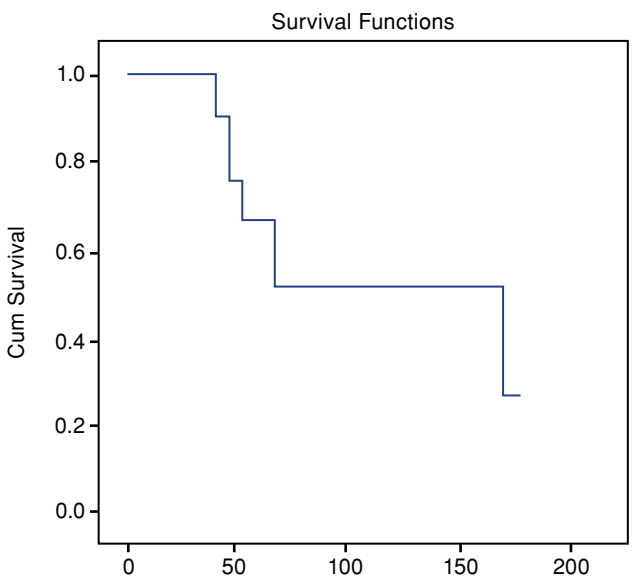

FIGURE 1. The Kaplan-Meier survival curve showing overall median disease-specific survival for the entire cohort.

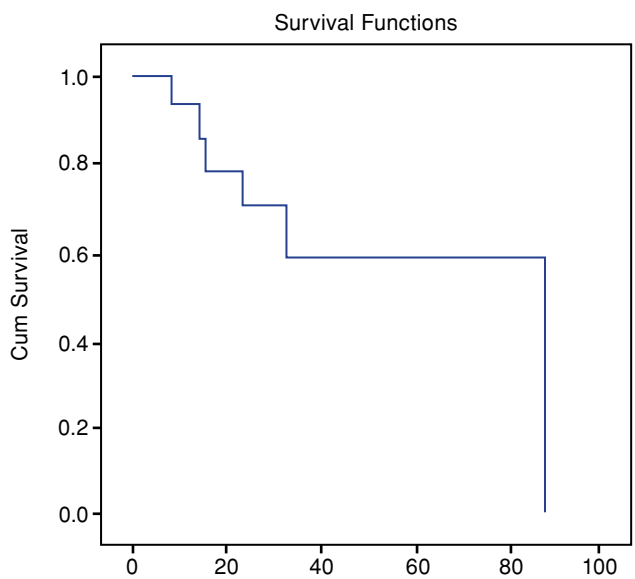

FIGURE 2. The Kaplan-Meier survival curve showing survival after bone metastases from endometrial cancer.

There was a statistically significant reduction in pain at the postoperative three-month VAS scores compared to baseline (from 8±0.9 to 2.8±0.6; p<0.001). All 14 (100%) patients reported pain relief after orthopedic surgery. The mean preoperative ECOG performance status for all patients reduced from 2.4±0.9 to 1.6±0.7 at three months postoperatively, indicating a statistically significant improvement (p<0.05). However, the ECOG performance status improved in only 10 of the 14 patients (71%).

Two (14.3%) patients developed complications such as wound dehiscence, and neither two of them needed debridement.

DISCUSSION

The presence of BMs is accepted to be a poor prognostic factor in a wide range of solid tumors, including breast and gynecological cancers.[18] However, with a small sample size of EC with BM patients, caution should be applied, as the number of metastasis and metastasis pattern may not be transferable to all patients. Some patients have solitary lower extremity or pelvic BM with the recurrence of the primary cancer with a more favorable metastasis. On the other hand, there are some high-grade patients with multiple organ involvement together with extra-pelvic bone with

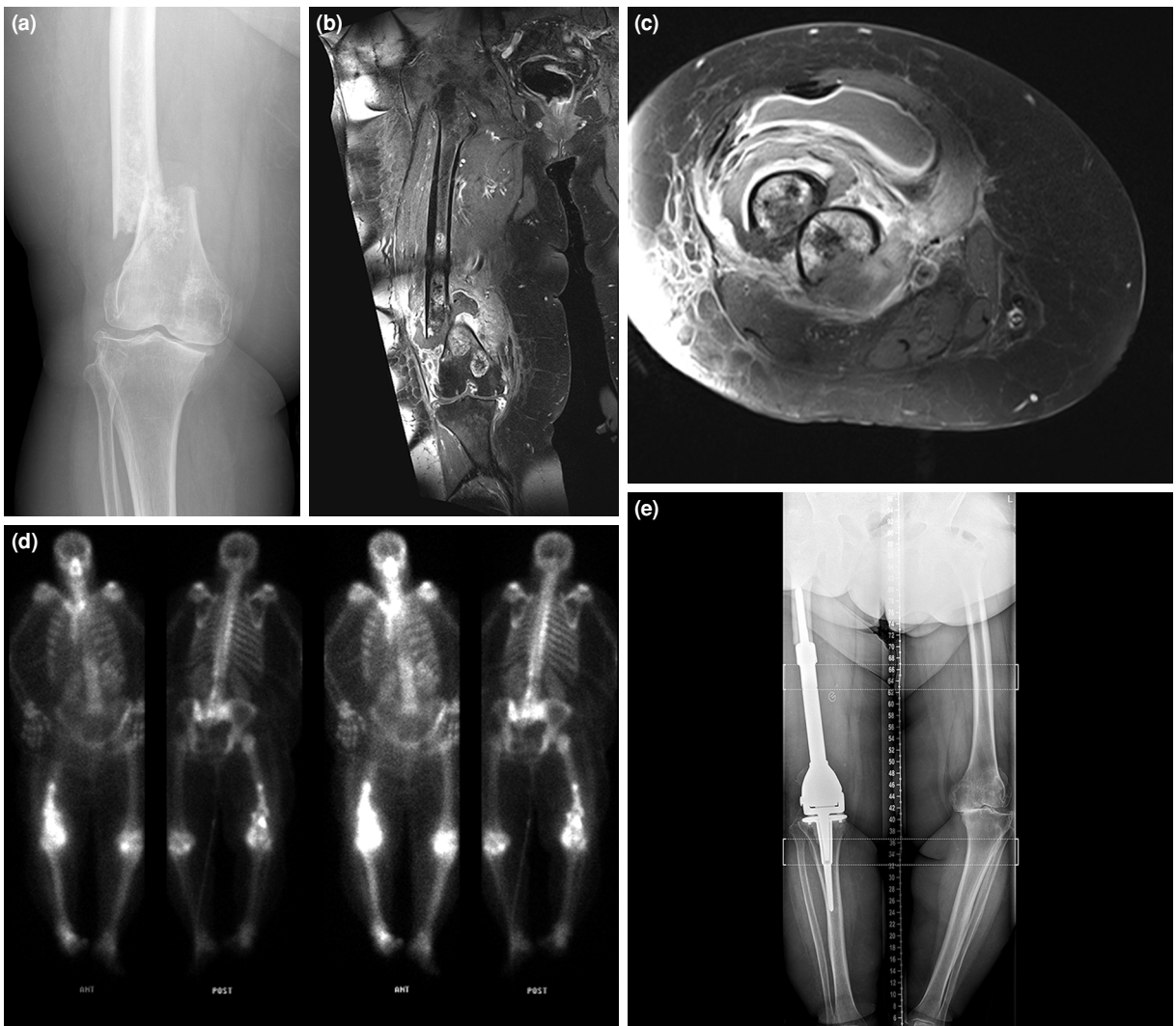

FIGURE 3. A 60-year-old female patient (Patient No. 2) was diagnosed with a metastatic endometrial adenocarcinoma to right distal femur presenting with a pathological fracture. **(a)** Right distal femur x-ray showing a pathological fracture with a calcified lesion. **(b)** Right femoral magnetic resonance imaging (T1 coronal+contrast) showing multiple bone lesions with cortical destruction and soft tissue extension. **(c)** Right femoral magnetic resonance imaging (T1 axial+contrast) showing adjacent soft tissue invasion and edema. **(d)** Total body bone scan showing the increased uptake from right distal femur. **(e)** A distal femoral endoprosthesis was used to reconstruct the bone defect.

aggressive features. These may consistently explain the poorer prognosis for these patients compared to those with solitary BM.

In the current study, the timing of BM was of utmost importance. Significantly longer overall survival was also reported in patients with BM at the time of recurrence compared to those patients with BM at diagnosis of EC.[19] Location of the metastasis is also another prognostic factor. Extra-pelvic metastasis and particularly solitary bone were significantly associated with longer overall survival.[19] Consistent with the literature, two patients in our series developed solitary-extra-pelvic BM in the femur and fibula, respectively 96 and 75 months after the initial diagnosis, they were both alive with no evidence of disease recurrence 74 and 84 months after resection of BM, respectively. Isolated lower extremity involvement was demonstrated in various case reports.[20-43] It may also occur as the first sign of EC without any history of vaginal bleeding or other gynecological symptoms.[6,7,23,25,27,30-35,37,38,40-54] Biopsy usually reveals an adenocarcinoma and the definitive diagnosis can be only made after diagnostic work-up for gynecologic cancers, such as abdominal ultrasound and uterine curettage.[41] Even if in this rare presentation without any gynecological symptoms of Stage IVB EC, the aforementioned authors reported good survival rates.

A review including more than 100 case reports revealed that shorter overall survival rates was observed in patients with lack of surgery (12 months), compared to surgical treatment for BM (42 months).[55] The radical treatment of solitary BM led to long-term survival in some patients. It may be concluded that the patients are in an oligometastatic state and wide surgical resection with adjuvant therapy can be curative. As shown in Figure 3, a low-grade patient with solitary BM and no other distant metastasis was treated with wide resection, and alive with no sign of disease.

Wide surgical resection may be a reasonable option for patients with solitary BM who do not have any extra-osseous disease, and who have the primary disease under control.[8] Palliative surgery for stabilization and pain with or without radiotherapy/chemotherapy is the treatment option for patients with multiple metastases.[18]

In the present study, we also emphasize the heterogeneity of the metastatic involvement in terms of location and the number of osseous metastases. These findings suggest that BM, particularly to the lower extremities, may be accepted as an oligometastatic state in EC. The most important issue in this context is the aggressive control of the osseous lesions in case of operability.[56] The main strengths of our study lie in the relatively large sample size and long-term follow-up.

Nonetheless, there are some limitations to this study. First, the single-center, retrospective design with a limited number of patients preclude to draw definitive conclusions. Second, even if all patients had the same primary tumor, there was a heterogeneity among surgeries and treatment modalities due to the individualized treatment modality based on decision of Multidisciplinary Tumor Council.

In conclusion, the possibility of BM should be always remembered in patients with musculoskeletal pain and should be evaluated to tailor a prompt treatment and to achieve a better prognosis. In our series, there were also multiple metastatic patients treated palliatively, as many of these patients had several comorbidities that prevented aggressive treatment procedures. These findings support the current clinical approach of aggressive treatment of single or oligometastatic disease and palliative treatment of EC patients with multiple involvements based on regarding patients' complaints or symptoms. According to the least number of patients and heterogeneity of the treatment modalities in metastatic EC, we cannot give a straight message; however, we can speculate that orthopedic oncologic interventions can improve the patient's quality of life when combined with other modalities. Further studies are needed to establish more reliable conclusions on this subject.

Ethics Committee Approval: The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (date: 17.06.2020, no: I5-311-20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: Z.O.B., M.O.K., H.Y.Y.; Design: K.B., M.O.K., K.B.; Data collection/processing: K.B.; Analysis/interpretation: Z.O.B., K.B., M.O.K., K.B.; Literature review: K.B., K.B.; Drafting/writing: K.B., M.O.K.,K.B.; Critical review: Z.O.B., H.Y.Y.

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