Bone Metastases of Endometrial Carcinoma Treated by Surgery: Report on 13 Patients and Review of The Medical Literature

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Abstract

Objective: The aim of this study was to describe the clinicopathological features of EC patients with bone metastases treated with surgery and to systematically review the literature.

Methods: We performed a retrospective study to include patients with bone metastases of EC at Peking University People's Hospital during 2000 to 2019. Clinicopathological features and survival outcomes were collected.

Results: Among the 1662 patients with EC, 14 (0.84%) were identified with bone metastases, and all were treated surgically. 13 cases were analyzed. Four had bone metastases when diagnosed; and the remaining 9 cases had bone metastases when first relapsed with the median time to recurrence of 13 months (range, 5-144). The median age of the 13 patients was 58 years old (range, 45-76). Twelve were endometrioid carcinoma. The majority sites of bone metastases were pelvis, followed by the spine. The median overall survival (OS) was 57 months. We further combined the 13 patients with another 24 cases identified from literature research. There was no significant difference in clinicopathological characteristics between the patients with bone metastases when diagnosed and when first relapsed. The median OS was numerically longer for patients with bone metastases when diagnosed than when first relapsed (57 vs. 36 months, P=0.084). The median OS was significantly longer in patients with endometrioid carcinoma than in those with type II carcinoma (57 vs. 4 months, P=0.003).

Conclusions: Patients with bone metastases of EC might benefit from comprehensive treatment based on surgery, as symptoms can be palliated and survival can be extended probably.

Introduction

EC is one of the most common gynecological cancer in the world, and its incidence has increased remarkably in recent decades, with approximate 63, 230 new cases in 2018[1].

In general, EC recurrence mostly occurs within the pelvis with the recurrence rate following initial treatment of around 11–13%[2]. EC is more likely to metastasize to the lymph nodes, liver and lungs[3], while bone involvement is quite rare and the prevalence is variously reported between 0% and 15%[4, 5]. The mechanism of metastasis of EC is thought to be related to hematologic dissemination by retrograde flow of tumor emboli or Batson's paravertebral valveless venous plexus[6]. However, the exact mechanism is not fully clear.

Bone metastases cause severe suffering to patients because of the severe pain, physical disability and pathologic skeletal-related events. Thus, early diagnosis and appropriate therapy are needed to enhance the quality of life (QOL) of patients with osseous dissemination. However, because of its rarity, factors influencing survival and optimal therapeutic regime of primary bone metastases in patients with EC are not known yet.

The main purpose of this study is to describe the clinicopathological features and treatment results of primary bone metastases of EC treated by surgery.

Materials And Methods

Patients

This was a retrospective study including EC patients with osseous disseminations. Patients diagnosed with EC were identified from January 2000 to December 2019 in Peking University People's Hospital. Afterwards, we particularly identified those patients who were diagnosed as primary bone metastases, including those who had bone metastases either at presentation with EC simultaneously or as the first site of recurrence (with or without concomitant extra-osseous lesions). Those with osseous dissemination that was subsequent locations of EC relapse were excluded. Patients with uterine sarcomas or carcinosarcomas were also excluded in this study. This study was approved by the Institutional Review Board of Peking University People's Hospital.

Follow Up

In the first year after surgery, the patients were examined every one to two months, then every three to six months for the next three years, and yearly afterwards, including routine and pelvic examinations, smear examination of the upper part of vagina, abdominopelvic ultrasonography, and evaluation of serous CA125. In the first two years, a chest X-ray was carried on every six months, and then every year in the next three years. If necessary, a thorough evaluation was applied making use of CT, MRI or PET scan of the chest, abdomen and pelvis.

Data Collection

Clinicopathological characteristics and survival outcomes of patients with primary bone metastases of EC were obtained from medical records. Patients were staged according to the 2009 FIGO (International Federation of Gynecology and Oncology) criteria. Description of tumor data was abstracted from primitive pathological reports.

Literature research

A comprehensive literature review was carried out systematically by searching for reports published from 1967 to present in the PubMed database, using the terms "bone metastasis" and "endometrial carcinoma". We screened all publications found in this field and chose those composed of clinical case series or

case reports that described patients with primary bone metastases of EC treated by surgical approach. Only papers reported in English were included.

Statistical analysis

Clinicopathological characteristics were analyzed using descriptive statistics and SPSS (version 24.0) was used for data management and statistical analysis. The median survival was estimated by Kaplan-Meier method. The OS after bone metastases was defined as the time from diagnosis of osseous dissemination to death or last follow-up. Statistically significant difference was defined as $P < 0.05$.

Results

Patient characteristics

Among the 1662 patients with EC diagnosed in Peking University People's Hospital during 2000 to 2019, 14 (0.84%) were identified with bone metastasis, and all of them were treated surgically. One patient was lost of follow-up after surgery. Therefore, the clinicopathological and survival data of the remaining 13 patients were finally reviewed. The characteristics of patients are described in detail in Table 1.

Table 1
Characteristics of 13 patients with primary bone metastases of EC treated by surgery at Peking University People's Hospital.

Pt. no.	Age (years)	Histology, grade, stage	Symptoms at presentation	CA-125 (u/ml)	Interval to bone met (months)	No. of bone met	Side	Localization	Extraosseous met	Palliative surgical resection	Adjuvant therapy after surgery	St
1	45	ADK,G2,IV	pain	84.62	9	1	Median	T12	Skin	Reconstruction	/	De
2	54	ADK,NA,NA	Pain	NA	38	1	Median	L2	No	Reconstruction	/	De
3	58	Clear cell,G3,II	Pain	NA	48	2	L	Acetabulum, L1	No	Reconstruction	/	De
4	76	ADK,NA,III	Pain	242.6	10	1	Median	L3	Lung	Reconstruction	RT	De
5	55	ADK,NA,NA	Pain	56.12	13	1	R	Tibia	Lung	Reconstruction	/	Liv
6	65	ADK,NA,NA	Pain	22.06	144	2	Bilateral	Ilium	No	Reconstruction	/	De
7	74	ADK,G2,I	Pain	7.79	13	3	R	Sacrum, ilium, L5	No	Reconstruction	/	Liv
8	54	ADK,G2,IV	Pain	14.31	At dx	2	L	Pubis, ischium	No	Reconstruction	RT + CHT + HT	De
9	56	ADK,G3,IV	Pain	64.74	At dx	2	R	Pubis, ischium	No	Reconstruction	RT + CHT	Liv
10	59	ADK,G3,IV	Pain	39.88	At dx	2	L	Pubis, ischium	No	Reconstruction	CHT	Liv
11	63	ADK,G1,I	Pain	NA	5	3	R	Acetabulum, pubis, ischium	Lung	Reconstruction	/	Liv
12	45	ADK,G3,IV	Pain	374.50	At dx	1	R	Pubis	Abdomen	Reconstruction	CHT	Liv
13	72	ADK,NA,NA	pain	204.50	36	2	R	Acetabulum, pubis	Lung	Reconstruction	/	Liv

Abbreviations: ADK, adenocarcinoma; CHT, chemotherapy; dx, diagnosis; HT, hormone therapy; L, left; met, metastases; NA, not available; Pt., patient; R, right; radiotherapy.

Among the 13 patients, 4 patients had bone metastases identified simultaneously with the diagnosis of EC. The remaining 9 patients had bone metastases at primary recurrence of EC, with the median time from diagnosis to bone metastasis of 13 months (range, 5-144 months). The median age was 58 years old (range, 45–76 years old). Except for one case of clear cell carcinoma, the remaining 12 cases were endometrioid carcinoma.

Characteristics Of Bone Metastasis

All cases were diagnosed according to symptoms, and all these patients had pain at the site of bones involved. The total locations of bone metastases were 23 in these 13 patients and the maximum amount of osseous dissemination found in a single patient was 3. The majority sites of bone metastasis were pelvic bones (17/23 sites), followed by the spine (5/23 sites). In five patients, the distribution of bone metastases involved the axial skeleton. Six patients had other metastases including the lung, the skin and the abdomen besides bone metastasis. Five patients had a single bone lesion, and eight had multiple bone metastases. Only 1 case was found to have a single bone site and no extra-osseous dissemination. All patients were treated with surgical resection with or without adjuvant therapy as the salvage treatment after osseous dissemination. Four cases were treated with chemotherapy with chemotherapy monotherapy

in two patients, chemotherapy plus radiotherapy in one patient and chemotherapy plus radiotherapy and hormone therapy in one patient. Six patients died of the disease at the date of data analysis. The median OS after diagnosis of bone metastases was 57 months.

Literature review

We further identified 20 studies[5, 7–25] with a total of 24 cases of EC patients with bone metastases treated by surgery through literature research. The detailed information of the included studies is displayed in Table 2. With addition of our 13 cases, a sum of 37 cases were further analyzed. We then stratified these cases into two groups: 24 cases with bone metastases when first relapsed and the other 13 cases with bone metastases when diagnosed as EC.

Table 2
Characteristics of 24 patients with primary bone metastases of EC treated by surgery reported in literature.

Author	Pt. no.	Age (years)	Histology, grade, stage	Symptoms at presentation	Interval to bone met (months)	Localization	Extraosseous met	Therapy	Status	Survival after bone met (months)
Ravault et al. [15]	1	61	NA,NA,NA	Pain	36	R tarsus	No	Surgery, RT	Live	7
Petru et al.[16]	2	61	ADK,G1,IV	Pain, swelling	At dx	L tarsus	No	Surgery, CHT, HT	Live	10
Clarke and Smith[17]	3	55	ADK,NA,NA	Pain, swelling	18	R talus, calcaneus	Lung	Surgery, RT	Dead	36
Mustafa et al. [18]	4	45	ADK,G2,I	Infection	36	Cranium	Lung, pelvic side wall	Surgery, HT	Dead	6
Neto at al.[19]	5	39	ADK,G2,IV	Pain, tumble	At dx	R ischium	No	Surgery, RT	Live	36
Arnold et al. [20]	6	63	ADK,G1,IV	Pain, leg weakness	At dx	T12	No	Surgery, RT, HT	Live	60
Ali et al.[21]	7	77	ADK,G3,I	Throbbing, swelling	24	L 4th toe, distal phalanx	Lung	Surgery, HT	Live	16
Haraguchi et al.[22]	8	87	NA,NA,NA	Pain	108	Sternum	No	Surgery	Live	60
Uharcek et al. [23]	9	67	ADK,G1,IV	Pain, erythema, swelling	At dx	R foot	No	Surgery, CHT, HT	Live	20
Albareda et al. [7]	10	62	ADK,G1,I	None	37	Sacrum	No	Surgery, HT	Live	26
Qin et al.[24]	11	48	ADK,G3,II	Pain	22	R and L femur	No	Surgery, CHT, HT, RT	Live	42
Pakos et al. [25]	12	62	ADK,G3,II	Pain	7	R tibia	No	Surgery	Live	27
Chan et al.[26]	13	62	NA,NA,NA	Pain	3	Sternum	NA	Surgery	Dead	18
Kehoe et al. [10]	14	58	ADK,G3,I	Pain	10	L4, L5	No	Surgery, RT, CHT	Live	199
Kehoe et al. [10]	15	60	Clear cell,G3,NA	Pain	12	Humerus, clavicle	No	Surgery, RT, CHT	Dead	13
Kehoe et al. [10]	16	55	ADK,G3,III	Pain	9	Rib	No	Surgery, RT	Dead	26
Kehoe et al. [10]	17	55	ADK,G3,IV	Pain	At dx	Ischium, acetabulum, femur	No	Surgery, RT	Dead	10
Jiang et al.[27]	18	51	ADK,G2,IV	Pain, swelling	At dx	L tibia, calcaneus, tarsus	Lung	Surgery, CHT, HT	Live	56
Vizzielli et al. [28]	19	62	ADK,G1,IV	Pain	At dx	Thigh, acetabulum, ischiopubic bone	Lung	Surgery, CHT	Live	30
Uccella et al. [11]	20	65	ADK,G2,IV	Pain	19	R sternum	No	Surgery, HT	Dead	60
Uccella et al. [11]	21	65	ADK,G2,NA	Lack of strength and sensation	18	T5	No	Surgery, RT, HT	Dead	9
Myriokefalitaki et al.[29]	22	57	ADK,G2,IV	Pain	At dx	R femur	No	Surgery, RT	Live	53
Kimyon et al. [30]	23	62	ADK,G2,I	Pain	2	Tibia, femur	No	Surgery, RT, CHT	Live	22
Makris et al. [31]	24	68	ADK,G1,IV	Pain	At dx	R tibia	No	Surgery, RT, CHT	Live	6

Abbreviations: ADK, adenocarcinoma; CHT, chemotherapy; dx, diagnosis; HT, hormone therapy; L, left; met, metastases; NA, not available; Pt., patient; R, right; and RT, radiotherapy.

We then compared the clinicopathological features and the survival outcome between the two groups. The overall characteristics of 37 patients are summarized in Table 3. In the 24 cases, the median interval from the diagnosis of the EC to osseous dissemination was 18 months (range, 2 to 144 months). The predominant histopathological type was endometrioid carcinoma. Presenting symptoms were bone pain, swelling, throbbing, weakness, erythema, infection, and lack of strength and sensation. Only 1 case was diagnosed as bone metastases without symptoms at the site involved. The most common affected location were the pelvic bones (23/59 sites [38.98%]). Bone recurrences were also seen in the vertebra, tarsus, talus, calcaneus, cranium, toe, sternum, femur, tibia, humerus, clavicle and ribs. At the diagnosis of bone metastasis, 11 (29.73%) patients had coexisting extra-osseous metastatic lesions, with the lung (9/11) being the most frequent.

Table 3
Overall characteristics of 37 patients with primary bone metastases of EC treated by surgery.

Characteristics	Bone metastases at primary recurrence of EC (n = 24)	Bone metastases at the diagnosis of EC (n = 13)	P value
Age, median (range), years	62 (45, 87)	57 (39, 68)	0.119
History			0.513
Endometrioid	19	13	
Nonendometrioid	2	0	
NA	3	0	
Cancer stage			/
I	7	0	
II	3	0	
III	2	0	
IV	2	13	
NA	10	0	
Grade			0.396
G1	2	5	
G2	6	4	
G3	7	4	
NA	9	0	
No. of bone lesions			0.985
Single	13	7	
Multiple	11	6	
Concomitant extraosseous metastases			0.708
Yes	8	3	
No	15	10	
Solitary bone metastasis without extraosseous involvement			0.501
Yes	8	6	
No	15	7	
Metastases to the axial skeleton			0.082
Yes	14	3	
No	10	10	
Overall survival, median, months	36.0	57.0	0.084
Abbreviations: NA, not available.			

There was no significant difference on clinicopathological characteristics and survival outcome between the two groups. The median OS after diagnosis of bone metastases for patients with bone metastases when first relapsed was 36 months, with the survival rate at 1-year, 2-year, and 5-year were 79%, 59%, and 31%, respectively, and the median OS for patients with bone metastases when diagnosed was 57 months, with the survival rate at 1-year, 2-year, and 5-year were 92%, 92%, and 46%, respectively. The median survival outcome of patients with bone metastasis when diagnosed was numerically longer than patients with bone metastasis when first relapsed, while there was no significant difference (P = 0.084). In addition, histology was a prognostic factor in patients with primary bone metastases of EC. The OS after bone metastasis was significantly longer in patients with endometrioid carcinoma than those with type II

carcinoma (57 vs. 4 months, P = 0.003). Other clinicopathological features, including age, number of bone lesions, concomitant extra-osseous metastases, single bone involvement and no extra-osseous spread, metastases to the axial skeleton, were not associated with survival outcome.

Discussion

In the present study, we described the clinicopathological characteristics and survival outcomes of 13 EC patients with bone metastasis. We further combined the 13 patients with the 24 cases with bone metastasis identified from literature research. We found that the median OS after bone metastases was significantly associated with histology.

The occurrence of osseous dissemination secondary to EC is rarely seen, and the incidence is unknown. Although autopsy data show an incidence up to 25%-27%[26], the clinical frequency is reported to be only 0.4%-1.8%[19, 22, 27]. Uccella et al[22] also pointed out that the incidence of osseous dissemination in EC was less than 1% according to literature review. While in Takeshita's cohort study[28], the incidence rate was up to 3.1%. The difference of sources of patients admitted to research centers might attribute to this distinction. In our series, the total incidence of bone metastases was 0.84%, and 0.24% in patients with bone metastases at presentation with EC.

Although with no significant difference statistically, the survival outcome was better for the patients with osseous dissemination as a presenting feature of EC than as a first site of recurrence (57 vs. 36 months) in our study. The same result has been reached in Vizzielli et al.'s[21] and Uccella et al.'s[22] research (28 vs. 21 months, and 20 vs. 10.5 months respectively). In addition, the limited sample size of this study may not be sufficient enough to obtain significant results, and further research is needed to determine the clinical significance of patterns of osseous dissemination.

At the time of diagnosis, most patients with bone metastasis had pain[25]. In our study, all patients presented with symptoms of pain, and in our literature review bone dissemination was discovered incidentally only in one case. The sacrum metastasis of the patient was found by conventional follow-up computed tomography scan 37 months after operation and confirmation was made by computed tomography-guided biopsy. Given the low incidence of bone metastasis, there is no routine assessment of bone dissemination in the surveillance of EC. While there is a need to have a suspicion for metastasis in EC patients presenting bone tenderness, and in patients with no history of cancer, but with osteodynia responding poorly to conservative management, as EC may be an underlying cause[4]. The initial diagnosis may be difficult since the symptom of bone pain is more common in benign diseases such as trauma, soft tissue inflammation, arthritis, and osteomyelitis[29]. While there is no standard approach to diagnose the bone disease, plain radiograph, bone scan, MRI, positron emission tomography (PET), aspiration cytology, and bone biopsy may help in the diagnosis. It is reported that technetium diphosphonate bone scans can be positive 18 months earlier before a lesion is detected on plain X-ray[30]. CT or MRI can be more helpful than bone scan, since these methods may be useful to help diagnose other metastatic locations, which could change the therapeutic scheme[19]. PET/CT scan is used to determine malignancies of bone lesions, similar to the CT scan for other malignant tumors, including breast cancer[31]. Therefore, we propose that clinical and radiologic assessment should be carried out for patients with suspected lesions to rule out bone metastasis.

Most of the tumors that metastasize to the bones are endometrioid[6], instead of those histologic subtypes supposed to be more aggressive, such as papillary serous or clear cell carcinomas. In our study, the predominant histopathological type was endometrioid (86%, 32/37), 57% (21/37) of the tumor were moderately or poorly differentiated, and 41% (15/37) were in FIGO stage IV. Some studies postulate that type II EC is associated with a worse prognosis[22, 27] and is a predictor of hematogenous dissemination in EC[32]. Our study reached the similar conclusion that endometrioid carcinoma was significantly associated with longer survival. It is suggested that EC with advanced stage and poorly differentiated grade is more likely to metastasize to bone[19]. Though rare, reports do exist concerning bone recurrence in early stage and well-differentiated EC[5].

In some literature, the axial skeleton was the predominant metastatic sites[19, 22, 27], while some researchers insisted that most bone metastases of EC affected the appendicular skeleton[21, 33]. Similar to Gunsu Kimyon's report[24], involvement of the axial (46%) and appendicular (54%) skeleton was almost equally observed in our study. It has been shown that 70% of cases had single localization bone recurrence and most patients had isolated bone metastases without extra-osseous spread[6, 23]. In the literature review, the most frequent sites of involvement were the vertebrate bones[33], with the pelvic bones being the second most common[19, 22]. In our series, most patients have metastases in a single bone site (54%) and the pelvic bones (39%) were the most commonly affected bones. At the same time of diagnosis of osseous dissemination, 11 (30%) patients had coexisting extra-osseous metastatic lesions, with the lung being the most frequent. In addition, Ucella et al. reported that patients with a single bone recurrence and the absence of extra-osseous spread have a better prognosis[22] and in some literature, outcome appeared to be more favorable in those patients with isolated bone metastases[4, 19]. However, we did not find a statistically significant relationship between these characteristics of bone metastases above and survival outcomes.

At present, the optimal therapeutic strategy has not been established yet for the patients with EC who developed bone metastases because of the few descriptions available in the literature due to their rarity and the various osseous sites being involved. Therapeutic schedules include surgical resection, directed radiotherapy, systemic chemotherapy, and hormonal therapy if hormone receptor positive. In accordance with literature from other solid tumors such as breast and prostate, another option as the treatment modality is bisphosphonate (zoledronic acid)[34]. The selection of regimen differs according to previous therapy, the number and location of bones involved, concomitant extra-osseous dissemination, and patients' performance status[27].

The impact of surgery management on survival outcome is not clear. Some researchers would argue that the tumor in the bone could just be a manifestation of a disseminated process and that it would be only a matter of time before other subclinical distant metastases became evident[35]. While the literature on the treatment of pulmonary metastases indicated that surgeons and oncologists treated some clinical criteria as minimal standard of operability. These guidelines involve the feasibility of a complete removal of the primary lesion and all pulmonary metastatic tumors and the absence of verifiable extrathoracic metastases. In these conditions, resection of the lung metastases seems reasonable[36]. Imitating the management, surgical resection of the bone metastases of EC may be justified. Thus, all patients were treated with wide resection and reconstruction to relieve symptoms palliatively, with or without adjuvant therapy in our study.

It is suggested that the radiotherapy works on most occasions and may be curative[4, 29]. In patients with single site bone metastasis, local radiotherapy is curative in deed, while chemotherapy will be applied first in patients with multiple locations. Therefore, it is a recommendation of a combination of radiotherapy and chemotherapy, which may be useful to control tumor volume[37]. After that, zoledronic acid is chosen to relieve bony pain, although it does not inhibit tumor growth[38]. With regard to the treatment in our series, most of the cases operated on were treated with adjuvant therapy, while the other few did not.

In review of the literature, a total of 37 cases who developed bone metastases of EC were treated by surgical approach with or without the adjuvant therapy, and the median survival was 57 months (range, 31–83 months). While according to previous literature reports, the median survival after the detection of osseous dissemination ranged from 10 months to 26 months[19, 21, 22]. Some experts reported that pain, pathological fracture and spinal cord compression were all indications for surgery[39] and pain control, a better performance grade, and improvement in QOL after operation of bone metastases were observed in deed[40]. Moreover, the aggressive operation may prolong the median survival by keeping a good QOL. Similarly, the median survival of the 19 patients with primary bone metastases of EC treated in Mayo Clinic was 12 months, and only one of them received complete surgical excision who survived 41 months after operation[22]. Currently, the issue of the best treatment plan remains controversial, but the main objective of treatment should be to palliate or even eliminate pain and extend survival. Taking the QOL into account, our case series may propose a probable therapeutic scheme of choice that the comprehensive treatment based on surgery be added to standard procedure for patients with bone dissemination of EC.

Our study was retrospective in nature, with the main limitations of the small study group and the heterogeneity of patients. Therefore, we acknowledge that it was not possible to draw any conclusions, but our results can be compared with assorted other published case reports in terms of clinicopathologic characteristics, treatment, and survival outcome.

Conclusions

Patients with primary bone metastases of EC might benefit from comprehensive treatment based on surgery, as symptoms can be palliated and survival can be extended probably.

Declarations

Ethics approval and consent to participate

The ethics committee of Peking University People's Hospital approved the study and the committee's number is 2020PHB331-01.

Availability of data and materials

The datasets generated and analysed during the current study are available in the Peking University People's Hospital repository.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Jingyuan Wang: Conceptualization, Investigation, Writing-original draft, Data curation. Yibo Dai: Formal analysis. Ji Tao: Resources. Wei Guo: Project administration. Zhiqi Wang: Writing-Reviewing and Editing, Funding acquisition. Jianliu Wang: Supervision, Funding acquisition.

Consent for publication

Written informed consent for the publication were obtained from the patients enrolled in our study.

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