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Bone metastases in endometrial cancer: Report on 19 patients and review of the medical literature☆,,☆☆

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Abstract

Objective—Because few cases of bone metastases of endometrial cancer have been reported, and information is scarce on their incidence, treatment, prognosis, and outcomes, we sought to compile a series of bone metastases of endometrial cancer and to systematically review the medical literature.

Methods—We retrospectively reviewed medical records of patients who had osseous metastases of endometrial cancer treated initially at Mayo Clinic (1984–2001), and of all patients who were referred for treatment of primary bone metastases after primary treatment for endometrial cancer elsewhere.

Results—Of 1632 patients with endometrial cancer, 13 (0.8%) had primary bone dissemination and 6 (0.4%) were referred after initial treatment. Three (15.8%) of these 19 had bone metastases at presentation; in the rest, median time to recurrence was 19.5 months (range, 3–114). The most common sites were the spine and hip. Median survival after metastasis was 12 months (range, 2–267). Median survival after radiotherapy alone vs. multi-modal treatment was 20 months (range, 12–119) vs. 33 months (range, 9–267), respectively (P > .99). Of the 87 caseswe reviewed from the literature, all but 1 (98.9%) had diagnoses based on symptoms. Multiple bone involvement and extraosseous dissemination were associated with poor prognosis. Type II endometrial cancer (i.e., serous or clear-cell histology) was associated with shorter life expectancy after diagnosis of bone metastasis compared to Type I tumors.

Conclusions—The incidence of primary bone metastases of endometrial cancer is <1%. Single bone metastases without extraosseous spread indicate less aggressive disease. Optimal treatment is unclear.

Keywords

Bone; Endometrial neoplasms; Neoplasm metastases; Osseous; Prognosis

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Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract in the US. Its estimated impact during 2011 was 46,470 newly diagnosed cases and 8120 deaths in the US alone [1].

In most cases, EC is confined at initial diagnosis to the uterus [2]. Nevertheless, nearly 1 in 3 women who die of EC is considered to have localized disease at the time of primary treatment [3]. There are 4 potential routes of dissemination in epithelial corpus cancer: 1) contiguous, 2) hematogenous, 3) lymphatic, and 4) exfoliation followed by intraperitoneal spread [4]. Most hematogenous failures occur in the lung or liver [5].

Bone metastases with EC are infrequent; their real incidence is unknown. Whereas anatomopathologic studies, including those of sub-clinical metastases detected only at autopsy, have an incidence as high as 25% [6], reports of only a few cases of bone metastases have been published [7–51]. In the largest series, Kehoe et al. [52] reported on 21 women with osseous dissemination. However, they made no distinction between bone metastases that were the first site of disease recurrence and those that were subsequent sites, and they provided no information on incidence and factors possibly associated with prognosis.

To estimate the real incidence and evaluate clinical outcomes, we reviewed and analyzed primary bone metastases (discovered either upon EC diagnosis or upon location of the primary site of recurrence) of patients treated at Mayo Clinic. We also conducted a comprehensive review of all available published reports on EC.

Materials and methods

A total of 1632 patients with EC were managed at Mayo Clinic, Rochester, Minnesota, between 1984 and 2001. Staging was defined according to the 1988 staging system of FIGO (Fédération Internationale de Gynécologie et d'Obstétrique [International Federation of Gynecology and Obstetrics]) [53]. Histologic classification was conducted according to that of the World Health Organization [54]. Architectural grading (i.e., the degree of glandular differentiation) was based on FIGO guidelines. Descriptions of tumor characteristics were abstracted from original pathology reports. A pathologist (G.L.K.) retrospectively reviewed all pathology slides (hematoxylin–eosin stain) of primary tumors to confirm original diagnoses (FIGO grade and histologic subtype).

Bone failure consisted of any case of EC metastatic to bone either at presentation with EC or as the primary site of recurrence (alone or in combination with other sites). Bone failure was diagnosed on the basis of clinical, radiographic, surgical, or histologic information in the medical record.

We separately considered patients who received primary treatment for EC elsewhere between 1984 and 2001, and who were referred to Mayo Clinic for treatment of primary bone metastases (as defined above). The referred cases were added to the series of patients who had initial treatment at Mayo Clinic.

All cases were reviewed by a radiologist (J.M.M.) to confirm the diagnosis of bone metastases made at imaging, when pathologic specimens were not available. Bone recurrences were then categorized as either having concomitant hematogenous, lymphatic, peritoneal, or vaginal sites of recurrence, or as consisting of isolated recurrence in 1 or more bones. Bone failures were categorized as having either single or multiple bone localizations. Patients with uterine sarcomas or carcinosarcomas were excluded.

At the discretion of the oncologist, patients with bone failure were treated selectively with radiotherapy or surgery to excise metastases; chemotherapy; hormonal therapy; or a combination.

At follow-up, information was abstracted from the clinical histories of patients. If survival and recurrence were insufficiently detailed, death certificates were obtained and patients and family physicians were contacted by letter or telephone for additional follow-up. Patients were censored if alive (with or without disease) at follow-up or if dead from an unrelated cause. For statistical analysis, we divided patients on the basis of tumor histology, comparing Type I endometrial cancer (defined as endometrioid cancer, endometrioid cancer with squamous differentiation, and adenosquamous cancer) with Type II endometrial cancer (defined as tumors with serous or clear-cell histology). Data on patients with grade 1 and grade 2 lesions were combined for comparison with data on patients with grade 3 lesions.

A systematic literature review was performed by searching the PubMed database for reports published between January 1, 1950, and May 31, 2011, using the terms “bone metast*” and “endometrial cancer”; “bone relapse” and “endometrial cancer”; “osseous dissemination” and “endometrial cancer”; or any combination thereof. We reviewed all publications identified in this search and selected those consisting of clinical case reports (including letters or abstracts) or case series that described patients affected by bone metastases of EC. A manual search of the references in each selected article was performed to identify additional reports of studies not captured by the online search that were potentially relevant for review. Only papers published in English, French, or Italian were considered. Abstracts presented at meetings were reviewed only if also published in indexed journals.

Statistical analysis was performed using the Fisher exact test (to evaluate the association between pairs of categorical variables), the Mann–Whitney *U* test (to test for differences between groups in the distribution of continuous measures), the Kaplan–Meier product-limit method (to determine survival curves), and the log-rank test (to identify predictors of disease-related survival). Statistically significant difference was defined as $P < .05$. For analysis, JMP statistical software (version 4.0.4; SAS Institute, Inc.) was used.

Results

Primary bone dissemination developed in 13 (0.8%) of the 1632 patients managed at Mayo Clinic for EC during the study period. Six other patients were referred to Mayo Clinic after receiving initial treatment elsewhere. Therefore, a total of 19 patients were included in the study, with a total of 29 identified sites of osseous metastases (the maximum number of bone metastases identified in a single patient was 4). The overall characteristics of patients are summarized in Table 1, and are described in detail in Table 2.

In 3 (15.8%) of the 19 patients, the diagnosis of bone metastases was made upon presentation with EC; 1 of these 3 patients was referred to Mayo Clinic after initial diagnosis of primary EC metastatic to bone. In the remaining 16 (84.2%) patients, the median time to recurrence was 19.5 months (range, 3–114 months). The diagnosis of bone metastasis was made more than 4 years after initial diagnosis of EC in 4 patients, 2 of whom had bone metastasis diagnosed more than 5 years later. The most common sites were the spine (13/29 sites [44.8%]) and the hip (4/29 sites [13.8%]). The sites of osseous metastatic localization are shown in Fig. 1. In 8 (42.1%) of the 19 patients, the metastases were on the right side, in 5 (26.3%) they were on the left, in 5 (26.3%) they were median, and in 1 (5.3%) they were bilateral, with no clear side prevalence.

All patients were symptomatic, and their symptoms warranted further clinical and radiologic assessment to rule out bone metastases. There were no cases of accidental diagnosis; pain at the site of osseous involvement was present in all 19 patients.

The median diameter of osseous lesions was 5 cm (range, 4–8 cm).

In 10 (52.6%) patients, histologic examination of the osseous lesion was consistent with endometrial primary tumor; in 3 (15.8%), cytologic sampling was positive for cells of adenocarcinoma compatible with cancer of the corpus uteri; and in 1 (5.3%), autopsy confirmed the diagnosis of EC metastatic to the bone after suspicion was raised by imaging studies. In the remaining 5 patients, diagnosis was based on radiologic findings. These cases were reviewed and confirmed by the radiologist.

The presence of extraosseous dissemination at diagnosis of bone metastases was detected in 9 (47.4%) patients, whereas multiple bone metastases were discovered in 6 (31.6%). Nine (47.4%) of the 19 patients had a single bone metastasis and no extraosseous spread, 4 (21.1%) had a single bone metastasis and presence of extraosseous dissemination, 1 (5.3%) had multiple (i.e., >2) bone metastases and no extraosseous dissemination, and 5 (26.3%) had both multiple skeletal metastases and extraosseous localizations.

Median survival after bone metastases was 12 months (range, 2–267 months). The presence of a single bone metastasis and no extraosseous dissemination was significantly associated with longer survival (26 vs. 6 months; $P = .008$) (Table 3). Overall survival was 18 months (range, 1–267 months) vs. 12 months (range, 6–14 months) for Type I vs. Type II endometrial cancer, respectively ($P = .70$). Of 10 patients without extraosseous spread, 9 had radiotherapy (alone or in combination); among these women, median survival for radiotherapy alone was 20 months (range, 12–119 months) vs. 33 months (range, 9–267 months) for multimodal treatment ($P > .99$). Surgical resection was attempted in 3 women, 2 of whom had no extraosseous spread. Complete surgical excision was obtained in 1 of these 2, with subsequent hormonal treatment with megestrol; this woman survived 41 months after surgical treatment before dying of recurrent bone disease in the proximity of the osseous excision.

Of the 8 (42.1%) patients who survived more than 2 years, all had Type I tumors; in particular, 7 (87.5%) had endometrioid EC, and 1 (12.5%) had adenosquamous histologic findings. In 5 (62.5%) of these 8, EC at initial diagnosis was poorly differentiated. Two (25%) of the 8 had bone metastases at presentation with EC (in both cases, bone metastases were single and without extraosseous spread). They survived 267 and 98 months, respectively. Six (75%) of these 8 patients received hormonal treatment with megestrol, either as the only treatment or in combination with surgery and/or radiotherapy and/or chemotherapy. The 3 women who survived more than 4 years after diagnosis of bone metastasis all received both radiotherapy and hormonal therapy.

Our review of the medical literature identified 46 studies [7–52] describing a total of 68 cases of EC metastatic to bone. Case reports with a maximum of 2 patients per study [7–51] are summarized in Table 4, whereas Table 5 summarizes the 21 cases included in the study by Kehoe et al. [52]. With the addition of our 19 cases, a total of 87 women were affected by osseous dissemination of EC. In 62 patients (43 in the literature and 19 from the present report), bone metastases were the primary site of relapse; in 4 patients, osseous dissemination occurred secondarily, after primary dissemination at another anatomical site; and in 21 patients (all in the same report) [52], bone metastases were not specified as primary or secondary. Of the 87 women whose cases we reviewed, 35 (40.2%) had metastases to the axial skeleton, 37 (42.5%) to the limbs, 6 (6.9%) to the cranium, and the

rest to a mixture of these sites. In only 1 (1.1%) case was bone metastasis diagnosed in the absence of symptoms at the site of metastasis (a sacral metastasis was discovered at a routine follow-up computed tomography scan 37 months after primary surgery and diagnosis was confirmed during computed tomography-guided biopsy). Twenty-eight women (32.2%) had diagnosis of bone metastases at initial presentation with EC. They survived longer than patients who received a diagnosis of bone metastases sometime after primary treatment for EC (median duration, 20 vs. 10.5 months; range, 2–267 vs. 1–199 months) ($P = .04$). This difference was also maintained when analysis was restricted to only those patients from studies describing only primary bone metastases (i.e., excluding the studies by Rocha et al. [48], Sahinler et al. [49], Amiot et al. [50], Oaknin et al. [51], and Kehoe et al. [52]): 24 months (range, 2–267 months) vs. 12 months (range, 1–119 months) ($P = .05$). Among patients with a diagnosis of bone metastases after primary treatment of EC, the median time between the onset of EC and the occurrence of osseous dissemination was 18 months. When osseous dissemination was diagnosed after primary treatment of EC, time to recurrence did not affect survival.

Of the 48 cases of primary bone metastases with available data regarding both tumor histology and survival, 42 had Type I and 6 had Type II histology. Overall survival after diagnosis of bone metastasis was 22 months (range, 1–267 months) among women with Type I EC and 6 months (range, 1–14) among women with Type II EC ($P = .02$).

Discussion

Bone metastases represent an unusual site of disease dissemination in patients with EC. With the present series, we were able to estimate the exact frequency of this type of event in the clinical setting, for an overall incidence of less than 1%. Bone metastases at presentation with EC are even more uncommon, representing only 0.12% of all patients with EC managed at our institution during the study period.

Although prior reviews have been published [22,25,27,33,41,47], the most updated review [41] captured only 29 cases of EC metastatic to bone. Little information on osseous dissemination of EC is available in the medical literature. An anatomopathologic study published in 1990 that reported data from 305 autopsies of women affected by gynecologic malignancies found 17 cases of bone metastases of EC [6]. All 17 women had concomitant extensive metastases elsewhere; therefore, it is likely that osseous involvement was a marker of disseminated, end-stage disease rather than the first site of relapse of the primary tumor. Fifteen (88%) of the 17 patients had bone metastases to the axial skeleton, either to vertebrae or pelvic bones [6].

A historical study on dissemination of EC noted 6 cases (2.3%) of bone metastases in 266 women [55]. The most common site was the axial skeleton, which was involved in 5 of the 6 (83%) patients. However, it is not clear whether the osseous spread in these 6 patients was the primary site of disease recurrence. Data from our series of 19 patients, despite being limited only to cases of bone metastases as the first localization of recurrent disease, are in agreement with those reported in this and other previous series: in fact, the spine and hip were the most common sites of osseous dissemination in our patients.

More recently, Kehoe et al. [52] published a clinical series in 2010 on bone metastases of EC diagnosed between 1990 and 2007 at Memorial Sloan-Kettering Cancer Center. They reported 21 cases of osseous dissemination of EC, by far the largest series on clinical outcomes until now. The spine was again the most commonly involved site, followed by the pelvic bones. The authors found a 10-month median survival after diagnosis of bone metastasis, which is comparable to the 12 months reported herein. However, Kehoe et al.

[52] included cases of later bone recurrence (i.e., bone recurrence not presenting as the first site of EC relapse). Moreover, they did not distinguish between patients initially treated at Memorial Sloan-Kettering Cancer Center and patients secondarily referred there, thus not providing information regarding the exact incidence of this type of metastasis in the general endometrial cancer population. Finally, multiple factors possibly associated with a worse prognosis were not analyzed, apart from the timing of recurrence and the presence of bone dissemination at diagnosis.

Our series illustrates how important it is to emphasize the poor survival of EC patients after diagnosis of bone dissemination (median, 1 year). This is somewhat discouraging if we consider that bone metastases represent a marker of clinically evident widespread metastatic disease in less than 50% of cases. In fact, in 53% of our 19 patients, the skeleton represented the only site of metastasis. However, patients with a single bone metastasis and no evidence of extraosseous disease had a significantly better prognosis than that of patients with more widespread disease.

No routine effort was made during the study period at Mayo Clinic to rule out the presence of bone metastases at the time of primary treatment for EC. Our findings justify this policy, given the low rate of bone metastases either at initial diagnosis or subsequently. Moreover, our literature review underscores the fact that only 1 of 91 cases of bone metastasis was discovered incidentally. Bone metastases are usually symptomatic. In a 1981 report on the routine use of radiographic bone surveys or bone scans during the management of 97 patients with EC [56], 3 cases (3%) of bone metastases were diagnosed; of these, 1 (1%) was found at initial diagnosis. No information was provided on the presence of symptoms accompanying the radiologic findings. However, the authors concluded that routine bone scans and surveys are not justified in patients with EC. Our own data are in agreement with these conclusions.

Both our series and our literature review suggest a better prognosis for patients whose bone metastases are discovered at presentation with EC than with later recurrence (20 vs. 10.5 months; $P = .04$), particularly when a single bone metastasis is present with no extraosseous dissemination. In fact, 2 of the 3 patients managed at Mayo Clinic who had a diagnosis of osseous spread concomitant with discovery of EC survived more than 7 years. The only patient with a poor prognosis had widespread multiorgan dissemination of metastatic disease; that patient survived only 2 months.

Another finding of our study is the fact that (as might be expected) women with Type II EC who have recurrence to the bone have a lower life expectancy than women with Type I histology.

The optimal elective treatment for bone metastasis of EC is unknown. This uncertainty is probably the result not only of the small number of cases described in the medical literature but also of the different osseous sites involved. Moreover, identifying the extraosseous sites of dissemination is crucial in determining possible therapeutic strategies. To eliminate at least this latter possible bias, we elected to analyze the type of treatment in our study group by focusing on cases without extraosseous spread. Although median survival seemed higher with multimodal therapy in terms of absolute numbers (33 vs. 20 months), statistical significance was not reached and no clear advantage over radiotherapy alone was evident.

Surgery was not related to dramatic improvement in oncologic outcomes, but the limited number of cases in the present series as well as in our literature review does not allow us to draw any definitive conclusions on this issue. Conversely, hormonal therapy with megestrol has been associated with good results, particularly in combination with other treatment

modalities. Again, we must emphasize that our data are too scant to support a strong recommendation on the best therapeutic approach for bone metastases of EC.

We must also acknowledge that our literature review is inevitably flawed by publication biases; that is, the published reports likely deal with the most unusual cases or those with the most favorable survival outcomes, thus not providing the real clinical picture of bone metastases of EC. Our series of 19 cases treated at the same institution strengthens the data and provides correction of possible biases.

In conclusion, we suggest that the real incidence of primary bone metastases of EC is low. Markers of better prognosis include the absence of multiple bone metastases and extraosseous spread, and the presence of bone localization at the debut of EC. Further research, including systematic study of progesterone receptor expression, should clarify whether hormonal therapy can have beneficial effects in such patients.

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Abbreviations

EC	endometrial cancer
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics)

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HIGHLIGHTS

- Bone metastases have an incidence of almost 1% in endometrial cancer patients.
- Diagnosis is almost invariably based on symptoms (mainly pain); routine bone scans during follow-up do not seem justified.
- Prognosis appears more favorable when bone metastasis is discovered at diagnosis of endometrial cancer.

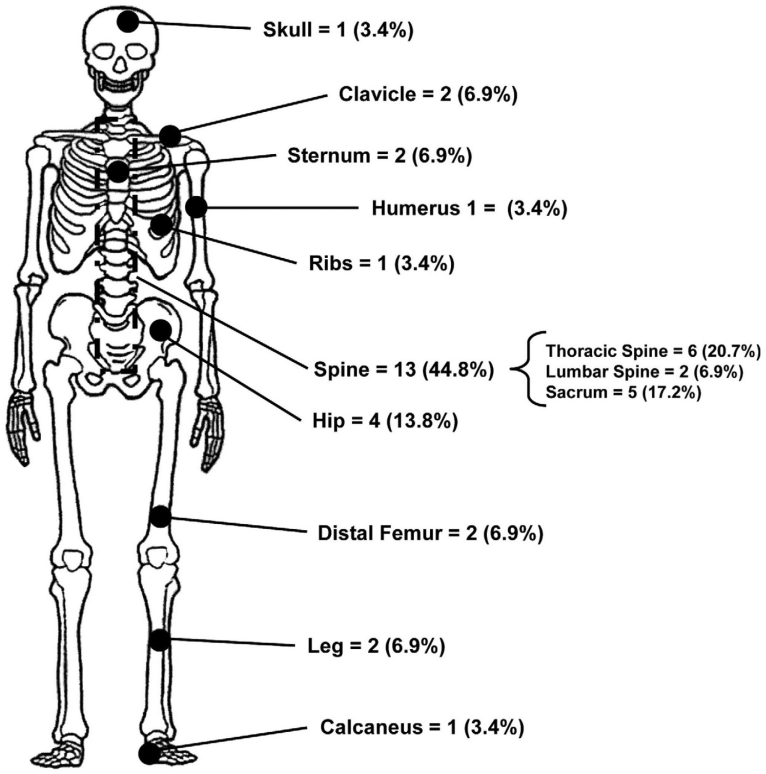

Fig. 1.

Sites of bone metastases in 19 patients with endometrial cancer. Twenty-nine osseous sites of metastasis were identified in 19 patients. Sites are shown independent of right/left location to avoid misinterpretation.

Table 1

Overall characteristics of 19 patients with bone metastases of endometrial cancer treated at Mayo Clinic.

Characteristic	No. (%)[a]
Age, median (range), years	65 (47–80)
Body mass index, median (range)	31 (17–43)
Histology	
Endometrioid	13 (68.4)
Nonendometrioid	6 (31.6)
Cancer stage	
I	10 (52.6)
II	1 (5.3)
III	3 (15.8)
IV	5 (26.3)
Estrogen and progesterone receptor on primary tumor[b]	
Positive	10 (52.6)
Negative	2 (10.5)
Missing data	7 (36.8)
Diagnosis at presentation of endometrial cancer	3 (15.8)
Time to bone recurrence (if diagnosis not made at presentation), median (range), months	19.5 (3–114)
Involvement of multiple bones	6 (31.6)
Concomitant extraosseous metastases	9 (47.4)
Patients with single bone involvement and no extraosseous spread	9 (47.4)
Overall survival, median (range), months	12 (2–267)
Missing follow-up data	2 (10.5)

[a] Values are number (percentage) unless indicated otherwise.

[b] Percentages total < 100% due to rounding.

Table 2

Individual characteristics of 19 patients with primary bone metastases of endometrial cancer treated at Mayo Clinica[a].

Pt. no.	Age	Histology, grade, stage[b]	Symptoms at presentation	Interval to bone met	No. of bone met	Side	Localization	Extraosseous met[c]	Therapy	Status	Survival after bone met
1	65 years	ADK, G2, IVB	Pain	19 months	1	R	Sternum (R margin)	No	Surgery, HT	DOD	60 months
2	65 years	ADK, G2, NA	Lack of strength and sensatior	l 8 months	1	Median	T5	No	Surgery, RT, HT	DOD	9 months
3	73 years	ADK, G3, IIB	Pain	4 months	2	R	Ischium, acetabulum	Lung	HT	DOD	28 months
4	71 years	ADK, G3, IC	Fracture	24 months	1	R	Tibia	No	RT, HT	DOD	25 months
5	66 years	Serous, G3, IIIC	Pain, inflammation	18 months	2	Median	T12, sternum	Brain, lung	Bisphosphonates	DOD	6 months
6	52 years	ADK, G3, IVB	Pain	7 months	2	R	Humerus, clavicle	Brain, cervical lymph node	RT, CHT	DOD	3 months
7	71 years	ADK, G3, IC	Pain	3 months	1	Median	Sacrum	Abdomen	RT	DOD	6 months
8	69 years	ADK, G3, IB	Pain	49 months	1	Median	Sacrum	Lung	HT	DOD	31 months
9	62 years	ADK, G3, IIIC	Pain	14 months	4	Bilateral	Skull, T4, T11, sacrum	Para-aortic nodes	RT	DOD	6 months
10	62 years	ADK, G2, IB	Pain, limp	20 months	1	L	Sacrum (sacroiliac joint)	No	RT, HT	DOD	11 months
11	70 years	ADK, G2, IB (adenosquamous)	Pain	20 months	4	L	Clavicle, ribs, T9, L3	Lung	RT	DOD	5 months
12	59 years	ADK, G1, IC	Pain	13 months	1	Median	T10	No	RT	NED	119 months
13	64 years	ADK, G2, IVB	Pain	At dx	1	R	Hip	No	RT, HT	NED	267 months
14	80 years	ADK, G3, IVB	Pain	Atdx	1	L	Sacrum (sacroiliac joint)	Widespread	HT	DOD	2 months
15	70 years	ADK, G3, IC	Pain	56 months	1	R	Femur	No	RT	DOD	26 months
16	60 years	Serous, G3, IB	Pain	34 months	2	L	Tibia, L3	No	RT	DOD	14 months
17	64 years	Serous, G2, IC	Pain, swelling	68 months	1	R	Calcaneus	No	RT	DOD	12 months
18	73 years	ADK, G3, IC	Pain	114 months	1	R	Femur	Lung	Surgery, RT, HT	DOC	8 months
19	47 years	ADK, G3, IVB (adenosquamous)	Pain	At dx	1	L	Hip	No	CHT, RT, HT	NED	98 months

Abbreviations: ADK, adenocarcinoma; CHT, chemotherapy; DOC, death by other causes; DOD, death by disease; dx, diagnosis; HT, hormone therapy; L, left; met, metastases; NED, no evidence of disease; Pt., patient; R, right; and RT, radiotherapy.

[a] For this summary table, we used the 1988 FIGO (Federation Internationale de Gynecologie et d'Obstetrique [International Federation of Gynecology and Obstetrics]) staging.

[b] For this summary table, we used the 1988 FIGO (Fédération Internationale de Gynécologie et d'Obstétrique [International Federation of Gynecology and Obstetrics]) staging.

[c] At the time of diagnosis of bone metastasis.

Table 3

Prognostic factors for survival after diagnosis of bone metastases of endometrial cancer in 19 patients treated at Mayo Clinic.

Characteristic	Survival, median (range), months[a,b]	*P* value
Multiple bone involvement		
Yes (n = 13)	6 (2–31)	
No (n = 6)	25.5 (9–267)	.006
Extraosseous disease		
Yes (n = 9)	6 (3–28)	
No (n = 10)	25 (2–267)	.087
Single bone involvement and no extraosseous disease		
Yes (n = 9)	26 (9–267)	
No (n = 10)	6 (2–31)	.008

[a] Values are median (range) unless indicated otherwise.

[b] Estrogen or progesterone receptor status and age at diagnosis were not associated with survival.

Table 4

Characteristics of 47 patients with primary or secondary bone metastases of endometrial cancer reported in case reports.[a]

Author, year	Pt. no.	Age	Histology, grade, stage[b]	Symptoms at presentation	Interval to bone met	Localization	Extraosseous met[c]	Therapy	Status	Survival after bone met
Primary bone metastases										
Ravault et al. [7]	1	61 years	NA, NA, NA	Pain	36 months	R tarsus	No	Surgery, RT	NED	7 months
Rouchy et al. [8]	2	61 years	ADK, G1, IVB	NA	At dx	L fibula	No	NA	NA	NA
Vanecko et al. [9]	3	67 years	NA, NA, I	Pain, limp	17 months	R fibula	No	RT	NED	12 months
	4	54 years	NA, NA, IVB	Pain	At dx	L fibula	No	RT	DOD	30 months
Janis and Feldman [10]	5	81 years	ADK, NA, II	Pain	36 months	L calcaneus	No	RT	NA	NA
Beller et al. [11]	6	59 years	ADK, G2, IC	Pain, inflammation	9 months	L femur	No	RT, CHT, HT	NA	NA
Zorzi and Pescatori [12]	7	80 years	ADK, G2, NA	Pain	10 months	R tarsus	No	Surgery	NA	NA
Onuba [13]	8	57 years	ADK, NA, IVB	Pain, fracture	Atdx	R tibia	Lung, kidney	NA	NA	13 months
Litton et al. [14]	9	55 years	ADK, G2, IB	Pain	24 months	R calcaneus	No	RT	NED	10 months
Maxymiw and Wood [15]	10	63 years	ADK, G3, IVA	Swelling	4 months	R mandible	No	RT	DOD	5 months
Cooper et al. [16]	11	59 years	ADK, G2, IVB (adenoacanthoma)	Pain, fracture	At dx	R calcaneus	No	RT, CHT, HT	NED	60 months
Nishida et al. [17]	12	61 years	ADK, G1, IIIB	Pain	2 months	L calcaneus	No	NA	NA	NA
Petru et al. [18]	13	61 years	ADK, G1, IVB	Pain, swelling	At dx	L tarsus	No	Surgery, CHT, HT	NED	10 months
Schols et al. [19]	14	66 years	ADK, G3, IA	Pain	18 months	R humerus	No	RT, HT	NED	24 months
Clarke and Smith [20]	15	55 years	ADK, NA, NA	Pain, swelling	18 months	R talus, calcaneus	Lung	Surgery, RT	DOD	36 months
Armentano et al. [21]	16	74 years	ADK, NA, IA	Pain, swelling	144 months	L tibia	No	None	DOD	1 month[d]
Malicky et al. [22]	17	44 years	ADK, G2, IVB	Pain	At dx	L femur	No	RT, CHT, HT	NED	24 months
Scott et al. [23]	18	50 years	ADK, G3, IIIC	Pain, mucocele	3 months	Paranasal sinuses	No	RT, CHT	NA	NA
Dosoretz et al. [24]	19	71 years	ADK, G2, IVB	Palpable mass	At dx	L mandible	No	RT, CHT	AWD	15 months
Mustafa et al. [25]	20	45 years	ADK, G2, IA (adenoacanthoma)	Infection	36 months	Cranium	Lung, pelvic side wall	Surgery, HT	DOD	6 months
Manolitsas et al. [26]	21	76 years	ADK, G3, IVB	Pain	At dx	R calcaneus	No	CHT, RT	DOD	19 months[e]
Neto et al. [27]	22	39 years	ADK, G2, IVB	Pain, tumble	At dx	R ischium	No	Surgery, RT	NED	36 months
Ali et al. [28]	23	77 years	ADK, G3, IC	Throbbing, swelling	24 months	L 4th toe, distal phalanx	Lung	Surgery, HT	AWD	16 months
Arnold et al. [29]	24	63 years	ADK, Gl, IVB	Pain, leg weakness	At dx	12th thoracic vertebra	No	Surgery, RT, HT	NED	60 months
Dursun et al. [30]	25	51 years	ADK, G3, IIIC	Pain	1 month	R and L humerus	Lymph nodes	RT	AWD	6 months
Ilvan et al. [31]	26	72 years	Clear cell, NA, IIB	Pain	14 months	Paranasal sinuses	Lung, liver	None	DOD	1 month

Author, year	Pt. no.	Age	Histology, grade, stage[b]	Symptoms at presentation	Interval to bone met	Localization	Extraosseous met[c]	Therapy	Status	Survival after bone met
Dursun et al. [32]	27	69 years	Clear cell, G3, IIIC	Pain	1 month	Widespread	No	CHT, HT	DOD	1 month
Giannakopoulos et al. [33]	28	68 years	ADK, G3, IVB	Pain	At dx	R ischium	No	RT	NED	48 months
Haraguchi et al. [34]	29	87 years	NA, NA, NA	Painful mass	108 months	Sternum	No	Surgery	NED	60 months
Landoni et al. [35]	30	66 years	ADK, G2, IIIA	Palpable mass	19 months	Rfoot	Vagina	RT	NA	NA
Loizzi et al. [36]	31	73 years	ADK, G3, IVB	Pain	At dx	R tibia	No	CHT	DOD	9 months[e]
	32	51 years	ADK, G3, IVB	Pain	At dx	Cervical vertebrae	No	CHT	DOD	2 months
Osanai et al. [37]	33	68 years	ADK, G3, IC	Pain	22 months	L ischium	No	CHT, bisphosphonates	NED	36 months
Uharcek et al. [38]	34	67 years	ADK, G1, IVB	Pain, erythema, swelling	At dx	R foot	No	Surgery, CHT, HT	NED	20 months
Kaya et al. [39]	35	70 years	ADK, G1, IVB	Pain, swelling	At dx	L tibia	No	RT	NED	47 months
Ishibashi et al. [40]	36	64 years	Carcinosarcoma, G3, IVB	Pain	At dx	R tibia	No	RT	DOD	6 months[f]
Albareda et al. [41]	37	62 years	ADK, G1, IB	None	37 months	Sacrum	No	Surgery, HT	NED	26 months
Farooq and Chang [42]	38	63 years	ADK, G1, IVB	Painful mass	At dx	Cranium, ribs, vertebrae	No	NA	NA	NA
Qin et al. [43]	39	48 years	ADK, G3, IIB	Pain	22 months	R and L femur	No	Surgery, CHT, RT, HT	NED	42 months
Pakos et al. [44]	40	62 years	ADK, G3, II	Pain	7 months	R tibia	No	Surgery	NED	27 months
Artioli et al. [45]	41	74 years	ADK, G3, IVB	Pain, infection	At dx	L tibia	No	RT, CHT	NA	NA
Chan et al. [46]	42	62 years	NA, NA, NA	Pain	3 months	Sternum	NA	Surgery	DOD	18 months
Jiang et al. [47]	43	51 years	ADK, G2, IVB	Pain, swelling	At dx	L tibia, calcaneus, tarsus	Lung	Surgery, CHT, HT	NED	56 months
Secondary bone metastases										
Rocha et al. [48]	44	67 years	NA, NA, NA	Painful mass	60 months	L mandible	Lung, kidney	Surgery	DOD	9 months
Sahinler et al. [49]	45	67 years	ADK, G3, IC	Pain, infection	4 months	R and L tibia, R and L	Vagina	RT	DOD	2 months
Amiot et al. [50]	46	86 years	ADK, G3, IIIC	Pain, infection	18 months	femur, L foot L hallux	Lung, bones (NS)	Surgery	DOD	NA
Oaknin et al. [51]	47	69 years	ADK, G1, IA	Pain	84 months	Spine	Vagina, deltoid	HT, CHT	DOD	5 months

Abbreviations: ADK, adenocarcinoma; AWD, alivewith disease; CHT, chemotherapy; DOD, death by disease; dx, diagnosis; HT, hormone therapy; L, left;met,metastases; NA, not available; NED, no evidence of disease; NS, not specified; Pt., patient; R, right; and RT, radiotherapy.

[a] Primary bone metastasis was defined as diagnosis of bone metastasis at the same time as diagnosis of endometrial cancer or as first site of recurrence; secondary bone metastasis was defined as second site of recurrence.

[b] For this summary table, we used the 1988 FIGO (Federation Internationale de Gynecologie et d'Obstetrique [International Federation of Gynecology and Obstetrics]) staging.

[c] At the time of diagnosis of bone metastasis.

[d] This patient refused treatment for primary disease, despite repeated recommendations and warnings by the attending physicians.

[e] No surgical treatment (i.e., hysterectomy plus bilateral salpingo-oophorectomy) was offered to this patient for management of primary disease of the uterus, because of her poor overall general health.

[f] This patient refused hysterectomy plus bilateral salpingo-oophorectomy and chemotherapy but allowed radiotherapy for the bone metastasis. She died of progressive disease.

Table 5

Characteristics of 21 Patients with primary or secondary bone metastases of endometrial cancer described by Kehoe et al. [52].[a]

Pt. no.	Age	Histology, grade, stage[b]	Symptoms at presentation	Interval to bone met	Localization	Extraosseous met[d]	Therapy	Status	Survival after bone met
1	61 years	ADK, G1, IIIA	Pain	44 months	Vertebrae	Yes (NS)	Surgery, RT	Dead[d]	12 months
2	65 years	ADK, G3, IIIB	Pain	3 months	Rib, vertebrae	Yes (NS)	CHT	Dead[d]	9 months
3	55 years	ADK, G3, IVB	Pain	Atdx	Ischium, acetabulum, femur	No	Surgery, RT	Dead[d]	10 months[e]
4	58 years	ADK, G3, IA	Pain	10 months	L4, L5	No	RT, Surgery, CHT	AWD	199 months
5	70 years	ADK, G3, IIB	Pain	10 months	Rib, vertebrae, parietal bone	Yes (NS)	RT	Dead[d]	2 months
6	65 years	ADK, G1, IIIB	Pain	7 months	Tibia	Yes (NS)	Surgery, NT	Dead[d]	42 months
7	47 years	ADK, G2, IVB	Pain	At dx	Vertebrae, femur, acetabulum, humerus	No	RT, CHT	Dead[d]	27 months
8	55 years	ADK,G1,NA	Pain	25 months	Pelvis, sacrum, vertebrae, rib	Yes (NS)	CHT	Dead[d]	7 months
9	60 years	Clear cell, G3, NA	Pain	12 months	Humerus, clavicle	No	Surgery, CHT, RT	Dead[d]	13 months
10	71 years	ADK, G2, IVB	Pain	16 months	L1, L3, L4	Yes (NS)	None	Dead[d]	1 month
11	74 years	ADK, G3, IB	Pain	8 months	Rib, vertebrae	Yes (NS)	RT, CHT	Dead[d]	5 months
12	62 years	ADK, G3, IVB	Pain	At dx	Vertebrae	Yes (NS)	RT, CHT	Dead[d]	16 months
13	62 years	ADK, G2, IIIC	Pain	11 months	Calvaria, femur, spine	Yes (NS)	Surgery	Dead[d]	54 months
14	60 years	ADK, G3, IVB	Pain	3 months	Sacroiliac joint	Yes (NS)	CHT, RT	Dead[d]	8 months
15	52 years	NA, NA, NA	Pain	148 months	Vertebrae	Yes (NS)	Surgery	Dead[d]	7 months
16	55 years	ADK, G3, IIIC	Pain	9 months	Rib	No	RT, surgery	Dead[d]	26 months
17	32 years	ADK, G3, IVB	Pain	At dx	Pubis, acetabulum	No	RT, CHT	AWD	5 months
18	40 years	ADK, G3, IIIC	Pain	3 months	Ischium	No	CHT	Dead[d]	10 months
19	84 years	ADK, G2, IVB	Pain	At dx	Ischium, pubis, acetabulum	No	RT	Dead[d]	34 months
20	77 years	ADK, G3, IVB	Pain	Atdx	Pubis, sacrum, acetabulum	Yes (NS)	RT, CHT	Dead[d]	8 months
21	56 years	ADK, G2, IC	Pain	26 months	Femur	Yes (NS)	Surgery, CHT	AWD[e]	12 months

Abbreviations: ADK, adenocarcinoma; AWD, alive with disease; CHT, chemotherapy; dx, diagnosis; L, left; met, metastases; NA, not available; NS, not specified; Pt., patient; and RT, radiotherapy.

[a]Primary bone metastasis was defined as diagnosis of bone metastasis at the same time as diagnosis of endometrial cancer or as first site of recurrence; secondary bone metastasis was defined as second site of recurrence.

[b]For this summary table, we used the 1988 FIGO (Fédération Internationale de Gynécologie et d'Obstétrique [International Federation of Gynecology and Obstetrics]) staging.

[d]At the time of diagnosis of bone metastasis.

[e]This patient refused hysterectomy plus bilateral salpingo-oophorectomy and chemotherapy but allowed radiotherapy plus surgery for the bone metastasis.