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

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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.

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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. multimodal treatment was 20 months (range, 12–119) vs. 33 months (range, 9–267), respectively ($P > .99$). Of the 87 cases we 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.

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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 subclinical metastases detected only at autopsy, have an incidence as high as 25% [6], reports of only a few cases of bone metastases have

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

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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).

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.

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