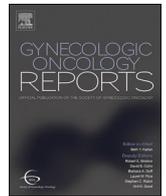




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Detection of bone metastases in uterine cancer: How common are they and should PET/CT be the standard for diagnosis?

Linda Hong^a, Laurin Cristiano^b, Eric Peters^c, Yevgeniya Ioffe^{d,*}

^a Department of Gynecology and Obstetrics, Division of Gynecologic Oncology, Loma Linda University School of Medicine, Loma Linda, CA, USA

^b Department of Gynecology and Obstetrics, Loma Linda University School of Medicine, Loma Linda, CA, USA

^c Department of Radiology, Loma Linda University School of Medicine, Loma Linda, CA, USA

^d Department of Gynecology & Obstetrics, Loma Linda University School of Medicine, 11175 Campus Street, Coleman Pavilion, Room 11105, Loma Linda, CA 92350, USA

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ABSTRACT

Objectives: Osseous metastases (OM) in endometrial cancer (EMCA) are thought to be rare. This study aimed to address the gap in present knowledge by defining the rate of OM in endometrial cancer (EMCA) as stratified by histology and ascertaining the best diagnostic modality for detection.

Methods: 435 consecutive cases of EMCA evaluated in tertiary care setting were reviewed. Clinico-pathologic data were abstracted and analyzed.

Results: 18/403 patients were found to have OM (4.6%). Majority were detected by PET/CT (13/18 (72%)), with conventional CT scans missing the diagnoses otherwise made by PET/CT scans in 2/9 patients. Patients with type II EMCA were at higher risk of developing OM compared with patients with type I EMCA; 2/234 patients with type I EMCA (0.85%) developed OM, as compared to 16/167 patients with type II EMCA (9.58%), OR = 12.3. Patients with serous histology had significantly higher odds of developing OM when compared to patients with non-serous histologies (OR 4, $p = 0.001$, 95% CI 1.54 to 10.76). Kaplan Myer survival function and log-rank analysis showed that the presence of OM was a significant negative prognosticator of survival, with median overall survival (mOS) of 16 months in OM patients vs. mOS undefined in non-OM patients ($p < 0.0001$).

Discussion: Incidence of detected OM was clinically significant, with most cases identified by PET/CT scans. Patients with type II EMCA, and in particular serous histology, were at a significantly higher risk of developing OM. OM when present, is an indicator of aggressive cancer biology and poor prognosis. Further studies are needed to ascertain the mechanism of predisposition to OM formation in serous EMCA and to confirm PET/CT as modality of choice for detection of OM.

1. Introduction

Endometrial cancer (EMCA) is the most common gynecologic cancer in high-income countries and a second most common gynecologic cancer worldwide with a lifetime risk of 2.9% (Siegel et al., 2019). 70% of patients have disease confined to the uterus at the time of diagnosis and exhibit excellent long term survival; (Lewin et al., 2010; Kimyon et al., 2016; Creasman et al., 1987). Recurrences are typically confined to the pelvis, and distant recurrences are seen primarily in the lymph nodes, lung, or liver (Kehoe et al., 2010).

EMCA can be further subdivide into type I and type II histologies with the latter comprising 10–20% of all new cases. Type I histology tends to be estrogen dependent and type II is non-estrogen dependent for

progression (Lax, 2016; Doll et al., 2008; Boruta et al., 2009). Type II cases have significantly worse prognosis than type I (Felix et al., 2010; Slomovitz et al., 2003; Thomas et al., 2007; CL, K. Cancer of the Corpus Uteri., in In SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 2007).

Osseous metastases (OM) in EMCA are thought to be rare with the prevalence reported anywhere between 0 and 15% (Kaya et al., 2007; Yoon et al., 2014; Neto et al., 2002). Studies suggest that a number of patients with OM are symptomatic with pain (Kimyon et al., 2016; Shigemitsu et al., 2010; Uccella et al., 2013). Studies of subclinical metastases detected only at the time of autopsy, report an incidence as high as 25% (Abdul-Karim et al., 1990; Abrams et al., 1950). This suggests that OM in endometrial cancer may be more common than

* Corresponding author.

E-mail address: yioffe@llu.edu (Y. Ioffe).

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originally believed. The choice of testing modality to elucidate the presence of metastatic disease may also influence the rate of detection.

There is paucity of information available regarding incidence of OM in type I vs type II disease and survival outcomes in those patients. In a study by Ucella and colleagues, a report of 19 patients with EMCA and OM and review of available literature, patients with type II (serous and clear cell histologies) had shorter overall survival when compared to patients with type I tumors (Uccella et al., 2013). The manuscript did not focus on the analysis of incidence/frequency of presentation by histology, however. The overall incidence of reported OM was very low in this group – <1% and vast majority of patients (99%) were symptomatic. Another manuscript that conducted a review of literature found higher incidence of OM in high-grade vs low-grade endometrial adenocarcinomas (Shigemitsu et al., 2010).

Isolated OM is associated with improved survival compared with extraosseous recurrence (Yoon et al., 2014). Early detection of OM could lead to earlier intervention and better quality of life (Shigemitsu et al., 2010). With the advances in imaging, it is possible that more of these early bone metastases could be detected prior to symptom onset.

Studies, even retrospective, of OM in endometrial cancer are few, with the largest single institution series reporting on 21 patients (Keheo et al., 2010), and there is little data to guide management. Routine screening for OM in endometrial cancer is not the standard of care and is not included in National Comprehensive Cancer Network (NCCN) algorithms for type I or type II histologies (Network, 2020).

Detection of OM with radiologic studies utilizes several pathophysiologic principles including increased metabolic activity, osteoblast activity, osseous lytic destruction or sclerosis, or alteration of marrow signal intensity. Previous studies have reviewed the comparative sensitivity and specificity of technetium 99 m Medronate (MDP) bone scan, Magnetic Resonance Imaging (MRI), F-18 Sodium Fluoride (F-18 NaF) Positron Emission Tomography/Computed Tomography (PET/CT), F-18 Fluorodeoxyglucose (FDG) PET/CT, and CT in detecting osseous metastatic disease for all types of malignancy. Their results demonstrated a slightly higher sensitivity for NaF PET and F-18 FDG PET/CT relative to MDP bone scan and CT (Bastawrous et al., 2014). However, NaF based scans are not commonly utilized due to high cost and limited scope of information. F-18 FDG PET/CT has previously been demonstrated to have high specificity (94–99%) and moderate sensitivity (65–67%) for detection of all site distant metastases in EMCA (Gee et al., 2018) and high sensitivity (98%), as well as modest specificity (56%) in detecting OM from all types of malignancies (O'Sullivan et al., 2015). Evaluation of the F-18 PET/CT for OM detection is readily available but has not been specifically addressed in the available literature.

In the current study, we aimed to quantify the prevalence of OM in EMCA with particular emphasis on tumor histology (type I vs II). In addition, we hypothesized that PET/CT may be a superior modality for OM detection in EMCA.

2. Methods

After obtaining approval from the Institutional Review Board at Loma Linda University Medical Center (LLUMC IRB), a retrospective cohort study was undertaken. Requirement for written informed consent was waived by the IRB.

New consults presenting to this practice, between April 1, 2013 to December 1, 2016 were identified. Patients were then followed to August 31, 2018 where data abstraction was performed and data set frozen. The study population selected for this investigation included women diagnosed with endometrial cancer who had imaging studies available for review including: radiographs, conventional CTs, and PET/CTs. We excluded patients under the age of 18 years old, patients with benign disease, those with malignancy other than endometrial cancer, and patients without available imaging studies or reports.

Abstracted data included age and stage at diagnosis, tumor histology, race, as well as presence of concurrent malignancies and personal

history of malignancies. Information on treatment received upon initial diagnosis of EMCA, and with recurrence(s) was collected. We also abstracted data pertaining to imaging modalities used for diagnosis and surveillance.

Presence of OM and the imaging modality used to make the diagnosis were abstracted. Treatment modalities received post diagnosis of OM were also recorded. Symptoms experienced at the time of diagnosis of OM were recorded. Patient outcomes including the length of median overall survival (mOS) and progression free survival (PFS) for all patients were recorded. If patients were lost to follow up, this was noted, as well as the length of follow up. For the patients who developed OM, length of survival post diagnosis of OM was recorded.

Available imaging studies were centrally reviewed by a LLUMC Radiologist specializing in Nuclear Radiology (E.P.) OM lesions were characterized as either lytic or blastic. EP confirmed the characterization of OM lesions or described them, if not previously noted.

For each subject, the best images available were utilized to determine the lytic or blastic nature of the lesions.

2.1. Statistical analyses:

Demographic data and patient characteristics were summarized. Patients were further sub-grouped by histologies. Odds ratio (OR) utilizing Fisher's exact test was calculated for development of OM for type I versus type II EMCA. In addition, OR for serous vs. non-serous histologies was calculated.

Subsequently, mOS was calculated for the two groups of patients: with and without OM. Kaplan Meier survival function and log-rank analysis were used to compare mOS for the two groups.

All data was analyzed utilizing Graph Pad Prism® statistical software (La Jolla, California).

3. Results

435 consecutive patient charts of women presenting to LLUMCC for evaluation of endometrial cancer were reviewed. Of these, 22 patients were excluded as they were identified as having malignancy other than endometrial cancer, benign disease, or were being duplicate records. 403 patients met criteria for inclusion.

The median age of endometrial cancer diagnosis was 64. 264 (66%) patients were White, 86 (21%) Hispanic, 26 (7%) Black, and 18 (5%) Asian, with 9 (2%) other/unknown.

249 (62%) patients presented with stage I disease, 24 (6%) with stage II, 70 (17%) with stage III, 48 with stage IV (12%), 4 (1%) with recurrence, and 8 (2%) with unstaged disease (Table 1).

3.1. Histology and OM

Histologies observed in this cohort were as follows: Type I EMCA (grade 1–2 endometrioid): 234 patients (59%), with 5 of those having synchronous ovarian cancers; Type II EMCA 167 patients (41%). The majority of type II patients had grade 3 and serous histologies. The breakdown of histologies are listed in Table 1.

18 of the 403 patients were found to have OM (4.6%). 6 patients presented with OM at initial diagnosis and 12 patients acquired the diagnosis of OM during progression or recurrence. Among patients with OM, 2/18 had grade 1–2 endometrioid EMCA (Type I EMCA), with 16/18 cases occurring in patients with Type II EMCA histologies (7 serous (including 1 mixed serous/clear cell); 4 grade 3 endometrioid (including one with serous foci), 1 poorly differentiated sarcoma; 1 carcinosarcoma; 3 poorly differentiated carcinomas). Of interest, the 2 patients with type I EMCA that developed OM, had stage I and II disease. Of the 16 patients with type II EMCA, 2 patients had stage I and II disease (findings summarized in Table 2).

Only 2/234 patients with type I EMCA (0.85%) developed OM, as compared to 16/167 patients with type II EMCA (9.58%). Patients with

Table 1
Patient demographics summarizing race, stage, histology and age upon presentation to care.

Race/Ethnicity	Stage at presentation	Histology	Type I vs. Type II	Age at presentation
White 264 (66%)	Stage I 249 (62%)	Endometrioid FIGO grade 1 + 2: 234 (58%)	Type I: 234 (58%)	24–38: 12 (3%)
Hispanic 86 (21%)	Stage II 24 (6%)	Endometrioid FIGO grade 3: 62 (15%)		41–50: 32 (8%)
Black 26 (7%)	Stage III 70 (17%)	Serous, including mixed histologies: 60 (15%)		51–60: 109 (27%)
Asian 18 (4%)	Stage IV 48 (12%)	Carcinosarcoma: 15 (4%)		61–70: 150 (37%)
Other/unknown 9 (2%)	Recurrent/unstaged 12 (3%)	Sarcoma: 11 (3%)		71–80: 86 (21%)
		Clear cell, including mixed histologies: 7 (2%)		82+: 14 (4%)
		Other high grade: 12 (3%)	Type II: 167 (42%)	Median: 64
		Undocumented: 2 (<1%)		
Total: 403(100%)	Total: 403 (100%)	Total: 403 (100%)	Total: 401 (100%)	Total: 403 (100%)
		Total = 403		n (%)
Age at Presentation (years)		24 – 40		12 (3)
		41– 50		32 (8)
		51– 60		109 (27)
		61– 70		150 (37)
		71–80		86 (21)
		82 +		14 (4)
		Median age: 64		
Race/Ethnicity		Asian		18 (4)
		Black		26 (7)
		Hispanic		86 (21)
		White		264 (66)
		Unknown/Other		9 (2)
Stage at Presentation		I		249 (62)
		II		24 (6)
		III		70 (17)
		IV		48 (12)
		Recurrent/unstaged		12 (3)
Histology		Endometrioid Grade 1–2		234 (58)
		Endometrioid Grade 3		62 (15)
		Serous		42 (10)
		Mixed serous		18 (4)
		Carcinosarcoma		11 (3)
		Sarcoma		7 (2)
		Clear cell (including mixed histology)		12 (3)
		Other high grade		2 (<1)
		Unknown		
Type I vs. Type II		Type I		234 (58)
		Type II		167 (42)
		Unknown		2 (<1)

type II EMCA were at a significantly higher risk of developing OM than patients with type I EMCA (OR = 12.29, p < 0.0001, 95% CI 2.98–54.35, Fisher’s exact test, Fig. 1).

When grouped by histology, patients with serous EMCA developed a disproportionately high number of OM (OR 4, p = 0.001, 95% CI 1.54 to 10.76, Fisher’s exact test) as compared to non-serous histologies patients. Fig. 2 demonstrates the distribution of OM among patient with serous (60 patients, 7 cases of OM) vs non-serous (343 patients, 11 cases of OM) histologies.

3.2. Location and lesion characterization of OM

In terms of skeletal locations of OM, 1/18 patients was noted to have OM in the extremity, the other 17 were found to have axial OM. 10/18 (56%) patients were noted to have lytic lesions on imaging, while 3/18 (17%) patients had blastic lesions. In 5 cases, definite lesions were seen but lesion type could not be characterized on review. The 3 patients with blastic lesion had high grade serous or mixed with clear cell histologies.

3.3. Survival outcomes

At last follow up conducted in August of 2018, 13 of the 18 (63%) of

patients with OM were dead of disease. 4 of 18 (22%) were alive and 1 patient was lost to follow up. The majority of patients without OM were alive at last follow up: 246/385 (64%). 46/385 (12%) were dead of disease, with 82/385 (21%) lost to follow up. Median OS was 16 months for patients with OM. In the group of patients without OM mOS was not reached. Kaplan-Myer function and log-rank analysis indicated that the presence of OM as a strong negative prognostic factor for length of mOS (p < 0.0001, HR 8.1, 95%CI 1.967 to 33.48, Fig. 4).

3.4. Role of PET/CT in diagnosis of OM

155 of 403 (38%) patients underwent PET/CTs during their treatment course. 13/155 patients assessed with this modality were found to have OM (8.4%) at some point in their disease course. Further details of timing of diagnosis are provided above and in Table 2.

In 18 cases of OM identification in this cohort, 9 patients (50%) underwent both PET/CT scan and conventional CT scans, while 5 patients had conventional CTs only, and 4 patients had a PET/CTs only. In total, 13 out of 18 (72%) patients underwent PET/CTs at diagnosis of OM. In 11 of the 13 patients who underwent a PET/CT, OM was considered positive based on imaging. 2 patients who had indeterminate results based on PET/CT, were further evaluated and ruled in with bone

Table 2
Clinical characteristics of 18 patients with endometrial cancer presenting with osseous metastasis.

Pt no.	Age (yrs)	Histology	FIGO stage*	Location of OM	Timing of OM	OM lesion on imaging	Biopsy of OM present	Survival post OM Dx (mos)	OS (mos)
1	52	Undifferentiated sarcoma	IVB	Bilateral iliac wings, ischium, T12	Diagnosis	Lytic	No	7	7
2	53	G1 endometrioid	IA	Right superior pubic ramus	Recurrence	Not characterized ^b	Yes	13	70
3	54	G3 endometrioid	IIIC1	Left side of L3, L4, L5	Recurrence	Lytic	No	5	60
4	59	Serous	IVB	T4, T7, T9, L2, R 7th rib, sternum, left sacrum	Diagnosis	Lytic	No	15	15
5	60	G3 endometrioid	IIIC1	Sternum, bilateral sternoclavicular joints, right clavicle, bilateral 1st and 2nd costochondral junctions	Recurrence	Lytic	Yes	1 ^c	10 ^e
6	60	Poorly differentiated	IVB	Right Isthium	Diagnosis	Lytic	Yes	14	14
7	61	Poorly differentiated	IVB	L3, L4, left hip and femur	Recurrence	Lytic	Yes	2	16
8	65	Serous	IVB	C1 transverse process	Progression	Not characterized ^b	No	17	24
9	66	Serous	II	Posterior left ilium	Recurrence	Not characterized ^b	No	18	18
10	68	Serous	IVB	L4 vertebral body	Diagnosis	Blastic	No	11	16
11	69	Mixed, clear cell 90%/serous 10%	IIIC1	Left sacrum	Recurrence	Blastic	Yes	6 ^c	16 ^c
12	70	Serous	IA	Left ischium	Recurrence	Blastic	Yes	23	35
13	71	G3 endometrioid	IVB	L3 vertebral body	Progression	Lytic	No	16	19
14	72	G3 endometrioid	IVB	C6, T9 costovertebral joint, L2 vertebral joints, ilium	Recurrence	Not characterized ^b	No	3 ^c	15 ^c
15	73	Serous	IVB	Right pubic symphysis, right posterior hip	Progression	Not characterized ^b	No	2	15
16	75	Poorly differentiated	IVB	Right tibia	Diagnosis	Lytic	Yes	32	32
17	76	Carcinosarcoma	IVB	Left ischial ramus	Diagnosis	Lytic	Yes	30	30
18	86	G2 endometrioid	II	T2, L4, right hemipelvis, left pubic symphysis	Recurrence	Lytic	No	3	8

Abbreviations: Dx, diagnosis; Mos, months; OM, osseous metastasis; OS, overall survival; Pt, patient; Yrs, years.

^aStaging based on the 2009 FIGO (International Federation of Gynecology and Obstetrics) staging.

^bLesion cannot be characterized on available imaging.

^cLost to follow up.

Incidence of Osseous Metastases (OM) in Type I vs. Type II Endometrial Cancers

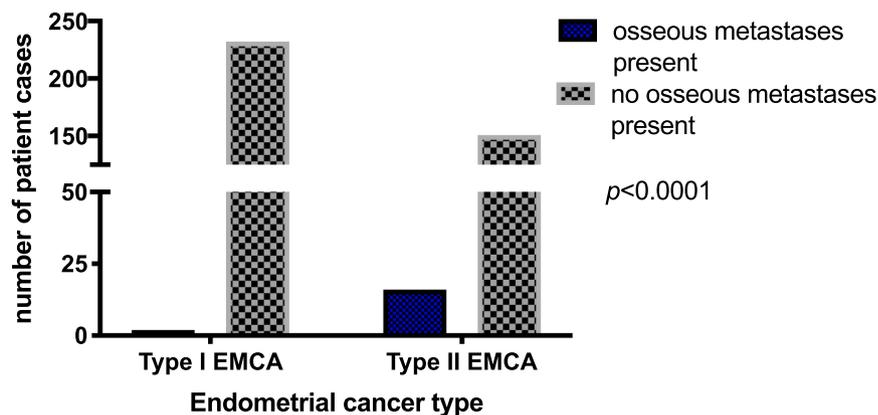


Fig. 1. Distribution of osseous metastases (OM) among patients with Type I, low grade (n = 234) and Type II, high grade (n = 167) endometrial cancers (EMCA) throughout their course of follow up. Patients with high grade EMCA developed a disproportionately higher number of OM 0.85% vs 9.58% ($p < 0.0001$, OR 12.3, 95% CI 3 to 54.4, Fisher's exact test).

biopsies.

Of the 9 patients who underwent a PET/CT and conventional CT scan, OM, otherwise identified by a PET/CT were not visualized in 3 patients by conventional CT. In 1 of the 3 cases of non-identification, the lesion was out of the CT standard field and thus not visualized. In the other 2 cases, conventional CTs did not visualize in field lesions otherwise visible by PET/CTs.

Fig. 3 compares the radiographic findings of a conventional CT scan and PET/CT scan of a patient with stage IVB serous endometrial cancer. The lesion is not visualized with conventional CT scan, but is clearly seen with PET/CT.

Incidence of osseous metastases (OM) in patients with serous vs. non-serous histology

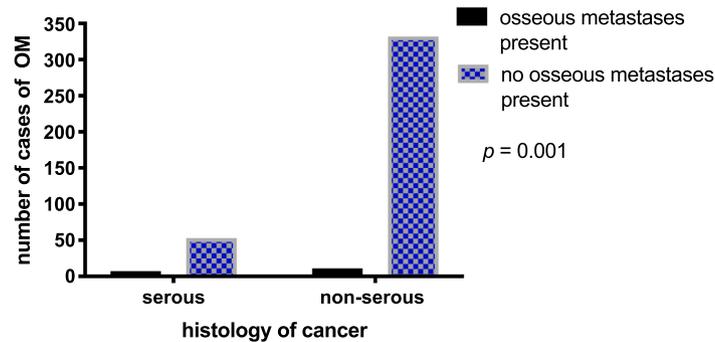


Fig. 2. Distribution of osseous metastases (OM) among patients with serous (n = 60) and non-serous (n = 443) endometrial cancers (EMCA). Patients with serous EMCA developed a disproportionately higher number of OM (p = 0.001, OR 4, 95% CI 1.54 to 10.76, Fisher's exact test).

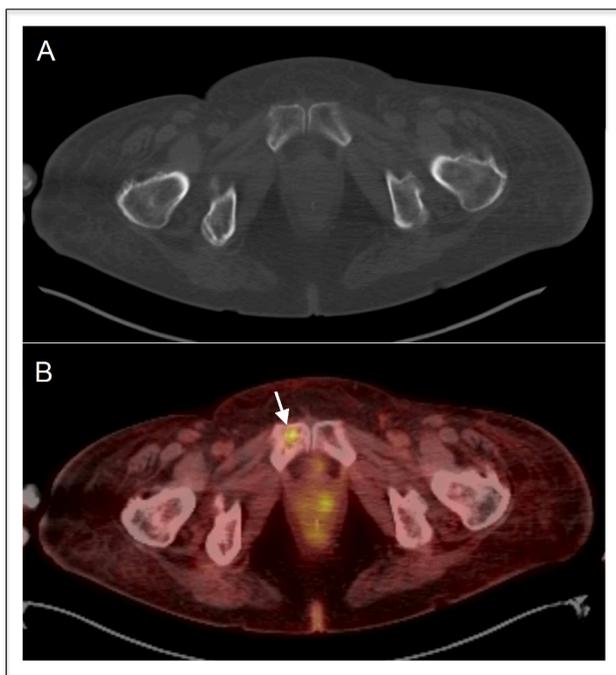


Fig. 3. Two imaging modalities of the same patient with stage IVB serous endometrial cancer and right pubic symphysis osseous metastases (OM). A) Axial CT image which does not demonstrate the right pubic symphysis (OM). B) Axial PET/CT image of right pubic symphysis lesion with metabolic activity (white arrow) with max SUV of 4.84 and measuring 1 cm.

4. Discussion

OM are considered to be uncommon in EMCA (Kaya et al., 2007; Neto et al., 2002; Shigemitsu et al., 2010; Shigemitsu et al., 2010), although limited older autopsy based studies may indicate otherwise (Abdul-Karim et al., 1990; Abrams et al., 1950). In this study, which collected detailed data from over 400 patients treated at a tertiary care institution, the rate of OM was 4.6%. The rate was comparable with previously reported rates in the literature, but higher than some of the fairly recent reports (Kehoe et al., 2010; Uccella et al., 2013).

A number of previous reports in the literature have demonstrated poor prognosis and morbidity associated with the manifestation of OM (Kehoe et al., 2010; Yoon et al., 2014; Shigemitsu et al., 2010; Uccella et al., 2013); The finding was confirmed by the current study, demonstrating that OM was a strong negative prognosticator of mOS (HR of

8.1, Fig. 4). Currently, there is no data whether early identification of OM could prolong patients' survival, but this may be the case, as some of our patients with otherwise asymptomatic OM noted diagnosed by imaging did exhibit long term survival. Other reports have concluded that treatment with radiotherapy and bisphosphonates may help with palliation and extension of OS (Shigemitsu et al., 2010). The question of best treatment modality and its influence on OS in patients with OM was beyond the scope of the current limited, retrospective study, but may be of interest and subject of larger, multi-center investigations.

Our study brought forth a concept that is yet to be well characterized in literature. We found that diagnosis of OM was strongly associated with type II EMCA histologies (more aggressive tumor phenotypes). In this study, the diagnosis of type II, as opposed to type I EMCA conferred over 100-fold risk of developing OM (9.58% vs 0.85%). Furthermore, when subdivided by histology, serous adenocarcinomas specifically were strongly associated with developing OM (Fig. 2). This appears to be a novel finding, highlighting the high-risk nature of serous histology further. Endometrial serous carcinomas are known to confer poor prognosis (Slomovitz et al., 2003; Hamilton et al., 2006; Cirisano et al., 2000; Creasman et al., 2006), but the predilection for development of OM is yet to be highlighted in the literature. The exact tumor biology leading to development of OM with this histology is yet to be addressed and will need to be addressed in further studies.

Currently, there are no recommendations for screening for OM either upon initial presentation for care with a diagnosis of EMCA or upon post-treatment surveillance. Based on the findings of this report, it may be reasonable to consider targeted screening for development of OM with PET/CT scans in patients with serous EMCA, and possibly other type II histologies. The frequency and duration of surveillance scans will need to be elucidated further. It seems that with the low risk of OM in patients with type I histology (0.85%), PET/CT surveillance can likely be safely omitted. PET/CT should, however, be considered in symptomatic patients, as the diagnosis can be missed by conventional CT scans.

The majority of OM disease identified in this cohort was detected by PET/CT, which has established superior sensitivity for metastatic disease including OM in many other disease entities (O'Sullivan et al., 2015). 13/18 OM in this study were detectable by F-18 FDG PET/CT. 5 of the subjects included in the study did not undergo F-18 FDG PET/CT to achieve the diagnosis of OM, as they had large lesions which were visible on conventional CT scans. It should be highlighted that 2 of 9 subjects with OM had clearly detectable lesions on the PET images without a corresponding detectable lesion on CT, suggesting that F-18 FDG PET/CT would be more sensitive than CT alone for detection of OM. This finding is limited by the small sample size of this study and exploratory nature of the analysis and thus precludes formulation of a robust conclusion or screening recommendations.

It should also be noted that PET/CT surveillance is not routinely

Survival of Endometrial Cancer Patients with and without Osseous Metastases (OM)

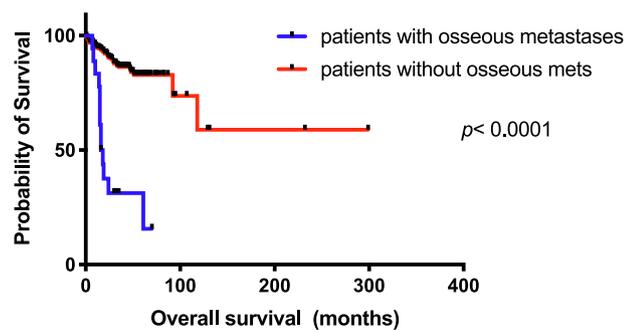


Fig. 4. Overall survival (OS) in months among patients with and without the presence of osseous (OM). Patients with OM, $n = 18$, had median OS of 16 months vs median OS not defined for patients without OM, $n = 385$ ($p < 0.0001$, HR = 8.1, 95% CI 1.967 to 33.48, logrank test).

recommended or practiced in the setting of endometrial cancer and as such the true prevalence of OM may be underrepresented in this cohort and also in the literature (Gee et al., 2018; Kitajima et al., 2010). Further research aimed at selective use of F-18 FDG PET/CT in surveillance of type II EMCA may highlight a higher OM rate in this patient group and further strengthen the role of F-18 PET/CTs as a surveillance modality of choice.

OM of the nonaxial skeleton was rare in our cohort with only 1/18 patients with OM in the extremity. This is generally consistent with report by Ucella et al, with patients exhibiting the majority of metastases along the vertebrae and the rest of axial skeleton. There's paucity of data in the literature regarding the type of OM noted on imaging (lytic vs blastic). In our patients, majority of patients had lytic lesions. The two patients with blastic lesions were noted to be patients with serous histology.

Our study had several intrinsic weaknesses. Due to the retrospective nature, exploratory analysis, and relatively small sample size, we cannot make definitive conclusions as to surveillance recommendations. Additional prospective studies will help determine whether routine surveillance with PET/CT should be considered in selected patients, such as those with serous histology.

We would like to conclude that OM was present in a clinically significant number of EMCA patients. We infer that in patients with high grade EMCA histology, development of OM at diagnosis or subsequent course should be considered and monitored for by the treating practitioner. In addition, screening with a more sensitive modality, i.e. F-18 PET/CTs may be considered, especially when serous histology is present. Targeted diagnostic strategies and their timing may be considered as a subject of future studies.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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