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Bone metastasis in endometrial cancer: evaluation of treatment approaches by factors affecting prognosis

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Summary

Objective: The purposes of this study were to present an endometrial cancer case with a first sign of bone metastasis, and to reveal factors affecting survival and the appropriate treatment methods for bone metastases. *Materials and Methods:* A total of 101 case reports that presented with bone metastasis of endometrial cancer were reviewed in this study. *Results:* Survival time in the patients without surgical treatment for bone metastasis was found to be 12 months (95% CI = 5.89 - 18.10) and 42 months in patients who underwent surgical treatment in addition to one or more of chemo-radio-hormonotherapies (95% CI= 16.58 - 67.41) (p=.006). Histological type of cancer, extra-osseous metastasis, and lack of surgery were the factors significantly affecting survival (p = 0.012, p = 0.002, and p = 0.038, respectively). *Conclusion:* Histological type and the presence of extra-osseous involvement are important prognostic markers in endometrial cancer patients with bone metastasis. It may be appropriate to implement combination therapies including surgery in the treatment of bone metastases.

Key words: Bone metastasis; Endometrial cancer; Prognosis.

Introduction

Endometrial cancer is the most common gynecological cancer in developed countries [1]. Most of the cases are diagnosed during early period; however, progressive disease typically metastases to pelvis, abdomen, and distant organs by direct invasion, lymph flow or intraperitoneal seeding [2]. One of the metastasis sites are the bones. Up to date, a total of 100 endometrial cancer cases with bone metastasis were reported in the literature [3-61]. While the incidence of primary bone invasion of endometrial cancer is not exactly known, it was reported as less than 1% [3]. Although there is evidence indicating a higher survival rate in isolated bone metastases of endometrial cancer by the assessment of case series, it remains still unclear which treatment method is appropriate for the treatment of the disease due to small number of cases.

The aim of the present study is to present an endometrial cancer case whose first sign was pain associated with fibula metastases and who had a pathological bone fracture without any gynecological complaints, and to review the important prognostic factors and suitable treatment methods with the compiled data on endometrial cancer cases whose bone metastasis were proven by pathological examination and/or radiological assessments.

Case Report

A bone fracture in left fibula was diagnosed in a 80-year-old patient who had the complaint of pain and swelling in her left ankle, and she was applied a plaster splint. However, no improvement was observed in the fracture during three month follow-up, and she underwent a bone biopsy considering pathological fracture. She was referred to a gynecology clinic with the doubt of metastasis of a gynecological malignancy following bone biopsy. On admission, there were no gynecological complaints of the patient. A swelling, erythema, and high temperature were detected at lateral to left ankle on malleol and inferolateral aspect of left knee. Pelvic examination was normal and ultrasonographic examination revealed that endometrium was irregular with seven to eight mm in the thickest part. Ca-125 level of the patient was found to be 220 U/ml and Ca19-9 level was 439 U/ml. Multiple lesions that may be compatible with metastasis in bilateral lungs were observed during chest tomography. Magnetic resonance imaging of the lower extremity revealed a 6×3×2 cm solid-cystic mass lesion on left fibula distal end, and a 11.5×10.5×7 cm solid-cystic mass lesion originating from left fibula proximal end with invading tibia and extending towards knee-joint and holding major neurovascular structures. In the whole-body bone scintigraphy, no other bone metastasis was observed. Endometrioid-type adenocarcinoma was diagnosed via endometrial sampling. Hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, and omentectomy were performed. An endometrioid-type adenocarcinoma grade-II disease including estrogen and progesterone receptors, showing full-thickness invasion into myometrium and reaching serosa was found in the postoperative uterine pathological examination. Carcinoma infiltration was observed in omentum of the patient with lymph node involvement at a macroscopic level. It was accepted as Stage IVB disease with lung metastases. Hormone therapy (megestrol acetate, 320 mg/day) was started with chemotherapy,

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following external pelvic radiotherapy (45 Gy) and vaginal brachytherapy (18 Gy). Left leg was amputated over the knee due to the complaint of worsening pain besides bone radiotherapy two months after the gynecologic operation (30 Gy). The patient died due to the progressively worsening disease at 13 months after the first admission and at ten months after the diagnosis.

Literature Review

PubMed and Embase databases (January 1, 1950 to June 1, 2014) were searched with terms as "bone metastasis and endometrial cancer", "bone metastasis and uterine cancer", "bone relapse and uterine cancer", "osseous dissemination and endometrial cancer" and "osseous dissemination and uterine cancer". Other than publications in English, translation of case reports in French and Italian languages were done by medical translators. It was possible to detect the articles which were not electronically available by examining the references of the available articles. A total of 100 case reports were found when the patients in two case series were added during literature review. Patients with the diagnosis of sarcoma and sarcomatous differentiation were not included into the study. The authors evaluated 101 cases including the present case (Table 1). Patient age, time from the onset of complaints until bone metastasis, time from bone metastasis until the detection of endometrial cancer, time from endometrial cancer diagnosis until the detection of bone metastasis, bone areas involved as a result of metastasis, extraosseous metastasis, its stages based on its description in case presentations, histological type, grading information, whether surgical staging was performed or not, bone biopsy, curettage, resection or amputation information, chemotherapy for metastasis, presence of radiotherapy and hormonotherapy and follow-up duration following bone metastasis, treatment outcome and survival times were compiled on a monthly basis. While patients with endometrioid adenocarcinoma, endometrioid cancer with squamous differentiation and adenosquameous cancer were classified as type I endometrial cancer and patients with clear cell, papillary serous cancer were classified as type II endometrial cancer cases. Grade I and II cases were grouped in low-grade cases group and grade III cases were in high-grade cases in the analyses.

Cases that underwent curettage, bone resection or extremity amputation for bone metastasis were accepted as surgically-treated cases. Only surgically-treated cases were defined as group I, cases who have taken one or more of chemo-radio-hormonotherapy (CRHT) options besides surgical treatment were defined as group II and patients who have taken CRHT without any surgical treatment were defined as group III and patients who could not be treated due to the impairment in general condition or who refused the treatment were defined as group IV.

SPSS version 15.0 (Statistical Package for Social Science, was used for statistical analysis. Survival following bone metastasis was defined as the time from the detection of bone metastasis until death. During survival analysis, survival curves were constructed by using Kaplan-Meier method based on the time from the detection of bone metastasis until death. Patients who survived at last follow up during the time until death were censored. Cox-regression analysis was used to describe independent prognostic factors that predicted survival regarding the disease. Statistical significance was defined as $p < 0.05$.

Results

Results of descriptive analysis

Data regarding 101 cases including the present case were collected. Median age of patients was found to be 63 years (range, 25-87) (n=100). Histological type of the cancer of six cases (6.2%) was non-endometrioid, two (2.08%) of the cases were defined as undifferentiated, and in five of the cases histological subtype was not available. Other cases were either defined as endometrioid (n=17; 17.7%) or adenocarcinoma (n=71; 73.9%) (n=96). There were 47 patients (53.4%) in the patient group with low grade (grade I = 19 cases and grade II = 28 cases) and 41 patients (46.6%) in the patient group with high grade cancer (n=88). Out of cases whose stage information was obtained, Stage I was reported in 23 (27.4%), Stage II in seven (8.3%), Stage III in 16 (19%), and Stage IV in 38 cases (45.2%) (n=84).

While the presence of bone metastasis was the first sign in 20 cases, bone metastasis was detected in 17 cases besides endometrial cancer diagnosis, 62 cases were admitted with bone recurrence, and this information was not available for two case (n=101). The time between the onset of complaints and the detection of bone metastasis (median duration of delay) was found to be three months (range, 1-16) (n=29). In five patients out of 20 whose first sign was bone metastasis, time from the histopathological identification of metastatic lesion until the detection of endometrial cancer was 6-36 months (6, 14, 42, 44, 60). Median value of the duration between endometrial cancer diagnosis and the emergence of recurrence in the bone was found to be 18 months (range, 2-148) (n=62). Median follow-up duration following bone metastasis was 12 months (range, 1-267) (n=88).

Most commonly affected bone areas were found to be hip (n=25), vertebra (n=21), feet bones (n=18), tibia (n=15), femur (n=11), head bones (n=10), sacrum (n=8), costa (n=8), humerus (n=6), sternum (n=4), fibula (n=4), and clavicula (n=3), respectively. Single bone involvement was present in 58 cases (57.4%) and multiple bone involvement was present in 43 cases (42.6%) (n=101). Whether it was single or multiple, it was observed that isolated bone metastasis was present in 47 cases (54%) and extraosseous invasion was present in 40 cases (46%) (n=87).

The presence of bone metastasis in 74 cases in the literature was confirmed by biopsy and the pathological examination of surgical specimens and autopsy materials. In the other cases, the presence of bone metastasis was approved by imaging methods without histopathological confirmation, or no information was given about this. At least one of the options such as curettage, excision, bone resection and amputation was performed for the treatment of bone metastasis in 38 cases (37.6%). Radiotherapy was used in 68 cases (67.3%), chemotherapy was used in 34 cases (33.7%) and hormonotherapy was used in 30 cases (29.7%) alone or in combination (n=101). Patient group which has taken only surgical treatment was composed of ten cases (group I, 9.9%), the group which has taken at least one of CHRT methods in combination with surgical treatment was composed of 28 cases (group II, 27.7%), the group which did not undergo any surgical treatment but taken at least one of CHRT methods was composed of 58 cases (group III,

Table 1. — *Detailed presentations of 101 cases reports of endometrial cancer with bone metastasis.*

Pt.No	Author,Year, No.	Age	Histology	Grade	Stage	Symptoms at presentation	Interval to bone met. (months)	Localization of bone met.	Extraosseous met.	Treatment of bone met.	Survival / Follow up after bone met. (months)	Status
1	Vanecko[5], 1967 1	54	Adenocarcinoma	NA	NA	Pain	PS	Fibula[c]	None	Surg,RHT	36	DBD
2	Vanecko, 2	67	Adenocarcinoma	NA	NA	Pain	17	Fibula[c]	None	RHT	12	AOD
3	Ravault[6], 1967	64	NA	NA	NA	Pain	36	Tarsus[c]	None	RT	16	AOD
4	Rouchy[7], 1967	60	Adenocarcinoma	G1	IVB	NA	PS	Fibula[c]	None	RT	7	AOD
5	Gelbermann[8], 1975	64	Adenocarcinoma	G1	NA	Pain	5	Tibia[c]	None	RT	NA	AOD
6	Janis-Feldman[9], 1976	81	Adenocarcinoma	NA	II	Pain	36	Calcaneus	None	RT	NA	NA
7	Bruffman[10], 1978	69	Adenocarcinoma	NA	NA	Pain	AD	Femur	None	RHT	NA	AOD
8	Litton[11], 1981	55	Adenocarcinoma	G2	IA	Pain, swelling	24	Ankle[c]	None	Surg,RT	10	AOD
9	Beller[12], 1982	59	Adenocarcinoma	G2	IC	Pain, swelling	9	Femur[c]	Lung	RCHT	NA	AWD
10	Boidi-trotti[13], 1982 1	70	NA	NA	NA	Pain	48	T4,T5 vert.	None	RT	NA	NA
11	Boidi-trotti, 2	55	NA	NA	NA	Pain	36	Knee	None	RT	1	NA
12	Zorzi-Pescatori[14], 1982	80	Adenocarcinoma	G2	NA	Pain	10	Tarsus	None	Surg	NA	NA
13	Onuba[15], 1983	57	Adenocarcinoma	G2	IVB	Pain	PS	Tibia[c]	Lung, Kidney, LN	RT	12	DBD
14	Le Iout[16], 1983	62	Adenocarcinoma	G3	NA	Pain	PS	Tibia[c]	LN	HT	7	AOD
15	Kapp[17], 1985	76	Adenosquamous	G1	IB	Compression	25	L5 vert[c]	None	Surg,RHT	NA	AOD
16	Schols[18], 1985	66	Adenocarcinoma	G3	IA	Pain	18	Humerus[c]	None	RHT	24	AOD
17	Maxymiw[19], 1991	63	Adenocarcinoma	G3	III	Swelling	8	Mandible[c]	LN	Surg,RT	4	DBD
18	Dosoretz[20], 1994	71	Adenocarcinoma	G2	III	Swelling	AD	Mandible[c]	None	Surg,RCT	15	AWD
19	Nishida[21], 1994	61	Adenocarcinoma	G1	IIIB	Pain	AD	Calcaneus[c]	None	CT	2	AOD
20	Cooper[22], 1994	59	Adenoacanthoma[a]	G2	IVB	Pain	PS	Calcaneus[c]	None	Surg,RCHT	60	AOD
21	Petru[23], 1995	61	Adenocarcinoma	G1	IVB	Pain, swelling	PS	Talus, calcaneus[c]	None	Surg	14	AOD
22	Clarke[24], 1996	55	Adenocarcinoma	G2	IVB	Pain	18	Ankle, talus, calc.[c]	Lung	Surg,RT	36	DBD
23	Giardina[25], 1996	55	Adenocarcinoma	G3	IV	Pain	14	Acetabulum[c]	Lung, LN	RT	1	DBD
24	Armentano[26], 1997	74	Adenocarcinoma	G1	IV	Pain, swelling	144	Tibia	None	None	1	DBD
25	Kushner[27], 1997	56	Endometrioid	G1	IC	Tenderness	15	9th rib	Lung	CT	3	DBD
26	Malicky[28], 1997	44	Endometrioid	G2	IVB	Pain	PS	Femur[c]	None	Surg, RCHT	24	AOD
27	Rocha[29], 2000	67	Adenocarcinoma	NA	IVB	Pain	60	Mandible[c]	Lung, kidney	Surg,CT	9	DBD
28	Sahinler[30], 2001	67	Undifferentiated	G3	IC	Pain	4	Metatarsal, tibia,fem.[c]	Vagina	RT	2	DBD
29	Mustafa[31], 2001	45	Adenocarcinoma[b]	G2	IA	Swelling	36	Frontal bone[c]	Lung, omentum, pelvic	Surg,HT	6	DBD
30	Manolitsas[32], 2002	76	Adenocarcinoma	G3	IVB	Pain	PS	Calcaneus[c]	Lung, LN	RCHT	19	DBD
31	Neto[33], 2002	39	Endometrioid	G2	IVB	Pain	PS	Ischium[c]	None	Surg,RT	36	AOD
32	Karamaz[34], 2002	67	NA	NA	NA	Pain	PS	Vert.	NA	RHT	NA	AOD
33	Creutzberg[35], 2002	NA	NA	NA	NA	NA	NA	NA	None	RT	36	AOD
34	Tang[36], 2002	25	Endometrioid[a]	G3	IV	Pain	PS	Ischium[c]	LN	RCT	48	AOD
35	Dursun[37], 2003	51	Endometrioid	G3	IIIC	Pain	AD	Humerus	LN	RT	6	AWD
36	Arnold[38], 2003	63	Adenocarcinoma	G1	IVB	Pain	PS	T12 vert.[c]	None	Surg,RHT	60	AOD
37	Ilvan[39], 2004	72	Clear cell	G3	IIB	Headache	4	Ethmoid, paranasal sin.[c]	Lung, liver, kidney	None	1	DBD
38	Loizzi[40], 2005 1	73	Undifferentiated	G3	IVB	Pain	AD	Tibia	Lung, bowel	CT	9	DBD
39	Loizzi, 2	51	Adenocarcinoma	G3	IVB	Pain	AD	Cervical vert.	None	CT	2	DBD
40	Amiot[41], 2005	86	Adenocarcinoma	G3	IIIC	Pain, redness	18	Hallux[c]	Lung, LN	Surg	NA	DBD
41	Dursun[42], 2006	69	Clear cell	G3	IIIC	Pain	AD	Bilat. fem.,multiple bone	LN	CHT	1	DBD
42	Kaya[43], 2006	70	Endometrioid	G1	1C	Pain	PS	Tibia[c]	None	RHT	47	AOD
43	Uharcek[44], 2006	67	Endometrioid	G1	IIIA	Pain, swelling	PS	Calc.,talus, m.tarsal[c]	None	Surg	20	AOD
44	Giannakopoulos[45], 2006	68	Endometrioid	G1	IVA	Pain	PS	Ischium[c]	None	RCHT	48	AOD
45	Landoni[46], 2006	66	Adenocarcinoma	G2	IIIA	Pain, swelling	18	Cuboid[c]	Pelvic	RT	NA	AWD
46	Osanai[47], 2006	68	Adenocarcinoma	G3	IC	Pain	22	Ischium[c]	None	CT	39	AOD
47	Haraguchi[48], 2006	87	Adenocarcinoma	NA	NA	Pain	108	Sternum[c]	None	Surg	60	AOD
48	Walrath[49], 2007	63	Adenocarcinoma	G1	IVB	Vision defect	72	Sphenoid bone	Lung, LN	RT	NA	AWD
49	Albareda[50], 2008	62	Endometrioid	G1	IB	Asymptomatic	37	Sacrum[c]	None	Surg,RHT	26	AOD
50	Qin[51], 2008	48	Adenocarcinoma	G3	IIB	Pain	22	Femur[c]	None	Surg,RCHT	42	AOD
51	Farooq[52], 2008	63	Endometrioid	G1	IVB	Headache	AD	Scalp, vert.,rib[c]	None	Surg	NA	AWD
52	Pakos[53], 2009	62	Endometrioid	G3	II	Pain	8	Tibia[c]	None	Surg	24	AOD
53	Chan[54], 2010	62	Adenocarcinoma	NA	NA	Pain	3	Sternum[c]	None	None	18	DBD
54	Artioli[55], 2010	74	Endometrioid	G3	IV	Pain,swelling	PS	Tibia[c]	Bowel	RCT	4	AWD
55	Shigemitsu[56], 2010	57	Endometrioid	G2	IVB	Pain	PS	Ischium,pubis[c]	Lung, LN	RCT	21	DBD
56	Kehoe[57], 2010 1	61	Adenocarcinoma	G1	IIIA	Pain	44	Vert.[c]	Yes	Surg,RT	12	DBD
57	Kehoe, 2	65	Adenocarcinoma	G3	IIIB	Pain	3	Rib, vert.	Yes	CT	9	DBD
58	Kehoe, 3	55	Adenocarcinoma	G3	IVB	Pain	AD	Hip[c]	None	Surg,RT	10	DBD
59	Kehoe, 4	58	Adenocarcinoma	G3	IA	Pain	10	L4, L5 vert.[c]	None	Surg,RCT	199	AWD
60	Kehoe, 5	70	Adenocarcinoma	G3	IIB	Pain	10	Rib, vert.,parietal bone	Yes	RT	2	DBD
61	Kehoe, 6	65	Adenocarcinoma	G1	IIIB	Pain	7	Tibia[c]	Yes	Surg,RT	42	DBD
62	Kehoe, 7	47	Adenocarcinoma	G2	IVB	Pain	AD	Vert.,fem., acet., hum.[c]	None	RCT	27	DBD
63	Kehoe, 8	55	Adenocarcinoma	G1	NA	Pain	25	Pelvis, sacrum,vert.,rib[c]	Yes	CT	7	DBD
64	Kehoe, 9	60	Clear cell	G3	NA	Pain	12	Humerus, clavicle[c]	None	Surg,RCT	13	DBD
65	Kehoe, 10	71	Adenocarcinoma	G2	IVB	Pain	16	L1,L3,L4 vert.	Yes	None	1	DBD
66	Kehoe, 11	74	Adenocarcinoma	G3	IB	Pain	8	Rib, vert.	Yes	RCT	5	DBD
67	Kehoe, 12	62	Adenocarcinoma	G3	IVB	Pain	AD	Vert.[c]	Yes	RCT	16	DBD
68	Kehoe, 13	62	Adenocarcinoma	G2	IIIC	Pain	11	Calvaria, fem.,vert.[c]	Yes	Surg	54	DBD
69	Kehoe, 14	60	Adenocarcinoma	G3	IVB	Pain	3	Sacroiliac joint	Yes	RCT	8	DBD

70	Kehoe, 15	52	Adenocarcinoma	NA	NA	Pain	148	Vert.[c]	Yes	Surg	7	DBD
71	Kehoe, 16	55	Adenocarcinoma	G3	IIIC	Pain	9	Rib[c]	None	Surg,RT	26	DBD
72	Kehoe, 17	32	Adenocarcinoma	G3	IVB	Pain	AD	Pubis, acetabulum[c]	None	RCT	5	AWD
73	Kehoe, 18	40	Adenocarcinoma	G3	IIIC	Pain	3	Ischium[c]	None	CT	10	DBD
74	Kehoe, 19	84	Adenocarcinoma	G2	IVB	Pain	AD	Ischium, pubis, acet.[c]	None	RT	34	DBD
75	Kehoe, 20	77	Adenocarcinoma	G3	IVB	Pain	AD	Pubis, sacrum,acet.	Yes	RCT	8	DBD
76	Kehoe, 21	56	Adenocarcinoma	G2	IC	Pain	26	Femur[c]	Yes	Surg,CT	12	AWD
77	Jiang[58], 2011	51	Adenocarcinoma	G2	IVB	Pain, swelling	PS	Tibia, calcaneus[c]	Lung	Surg	56	AWD
78	Vizzielli[59], 2011	62	Adenocarcinoma	G2	IVB	Pain	PS	Hip[c]	Lung	Surg,CT	30	AOD
79	Gottwald[60], 2011	59	Endometrioid	G2	II	Pain, swelling	43	Tibia, humerus[c]	None	Surg,RT	NA	AOD
80	Ucella[3], 2013 1	65	Adenocarcinoma	G2	IVB	Pain	19	Sternum[?]	None	Surg,HT	60	DBD
81	Ucella, 2	65	Adenocarcinoma	G2	NA	Lack of strength	8	T5 vert[?]	None	Surg,RHT	9	DBD
82	Ucella, 3	73	Adenocarcinoma	G3	IIB	Pain	4	Ischium, acetabulum[?]	Lung	HT	28	DBD
83	Ucella, 4	71	Adenocarcinoma	G3	IC	Fracture	24	Tibia[?]	None	RHT	25	DBD
84	Ucella, 5	66	Serous	G3	IIIC	Pain	18	T12 vert., sternum[?]	Brain, lung	Biph	6	DBD
85	Ucella, 6	52	Adenocarcinoma	G3	IVB	Pain	7	Humerus, clavicle[?]	Brain, cervical LN	RCT	3	DBD
86	Ucella, 7	71	Adenocarcinoma	G3	IC	Pain	3	Sacrum[?]	Abdomen	RT	6	DBD
87	Ucella, 8	69	Adenocarcinoma	G3	IB	Pain	49	Sacrum[?]	Lung	HT	31	DBD
88	Ucella, 9	62	Adenocarcinoma	G3	IIIC	Pain	14	Skull, T4,T11vert. sacrum[?]	Para-aortic LN	RT	6	DBD
89	Ucella, 10	62	Adenocarcinoma	G2	IB	Pain, limp	20	Sacrum[?]	None	RHT	11	DBD
90	Ucella, 11	70	Adenocarcinoma[a]	G2	IB	Pain	20	Clavicle, ribs, T9, L3[?]	Lung	RT	5	DBD
91	Ucella, 12	59	Adenocarcinoma	G1	IC	Pain	13	T10 vert.[?]	None	RT	119	AOD
92	Ucella, 13	64	Adenocarcinoma	G2	IVB	Pain	AD	Hip[?]	None	RHT	267	AOD
93	Ucella, 14	80	Adenocarcinoma	G3	IVB	Pain	AD	Sacrum[?]	Widespread	HT	2	DBD
94	Ucella, 15	70	Adenocarcinoma	G3	IC	Pain	56	Femur[?]	None	RT	26	DBD
95	Ucella, 16	60	Serous	G3	IB	Pain	34	Tibia[?]	None	RT	14	DBD
96	Ucella, 17	64	Serous	G2	IC	Pain, swelling	68	Calcaneus[?]	None	RT	12	DBD
97	Ucella, 18	73	Adenocarcinoma	G3	IC	Pain	114	Femur[?]	Lung	Surg,RHT	8	DBC
98	Ucella, 19	47	Adenocarcinoma[a]	G3	IVB	Pain	AD	Hip[?]	None	RCHT	98	AOD
99	Myriokefalitaki[61], 2013	57	Endometrioid	G2	IVB	Pain, fracture	PS	Hip[c]	None	Surg,RHT	53	AOD
100	Nguyen[62], 2013	56	Endometrioid	G1	IVB	Pain	NA	Ischium[c]	Muscle, LN	RCT	9	AWD
101	Doger (Ourcase), 2014	80	Endometrioid	G2	IVB	Pain, swelling	PS	Fibula, tibia, ankle[c]	Lung, LN	Surg,RCHT	13	DBD

[a] With adenosquamoz histological component, [b] With adenoachantoma histological component, [c] Diagnosis confirmed by bone biopsy, [?] It's not clear whether the diagnosis of bone metastasis is based on either bone biopsy or radiographic imaging (in 12 cases the diagnosis was based on histological examinations and in five cases was based on radiographic imaging).

Abbreviations: Pt patient, No number, Met metastasis, AD At diagnosis (The diagnosis of endometrial cancer and bone metastasis were diagnosed at the same time), PS presenting symptom (The patients were presented with bone metastasis), Acet acetabulum, Calc calcaneus, Hum humerus, Fem Femur, Vert vertebrae, LN lymph node, Surg surgery, RT radiotherapy, CT chemotherapy, HT hormone therapy, Biph Biphosphonate, AOD alive without disease, AWD alive with disease, DBD death by disease, DBC death by other causes, NA not available (The ranking was based on publishing years of cases).

57.4%), and the group which did not or could not take any treatment was composed of four cases (group IV, 3.9%), and one patient underwent only biphosphonate treatment (n=101). The number of patients who used at least one or more of CHRT was 86 (85.1%).

Outcomes of 97 patients could be obtained and 32 patients were found to be alive without disease, 12 patients were alive with disease, and 52 patients were dead because of disease. One patient was dead due to causes not specified by the disease. Median time from the detection of bone metastasis until death was found to be nine months (range, 1-60) (n=52). Patients with extraosseous metastasis were excluded from the analysis and median time from the detection of bone metastasis until death was found to be 13.5 months (range, 1-60) (n=16).

Results of survival analysis

The presence of multiple bone involvement was found to be a factor that significantly affects survival. In case of single bone involvement (n=25) median estimate survival was 26 months (95% CI = 10.59 - 41.40) and it was 13 months (95% CI = 7.43 - 18.56) in the presence of multiple bone involvement (p = 0.031) (Figure 1). The presence of extraosseous metastasis was another important factor that significantly affects survival. While median estimate survival was found to be 36 months (95% CI = 0.00 - 76.62) in cases with isolated bone metastasis (without extraosseous metastasis) (n=22), it was found to be nine months (95% CI = 5.21 - 12.87) in the presence of extraosseous metastasis (n=36) (p < 0.001) (Figure 2).

Survival time for the patients with type I endometrial adenocancer (n=46) was 26 months (95% CI = 16.39 - 35.60) and it was six months (95% CI = 0.00 - 19.20) in patients with type II cancer (n=6) (p = 0.004). Median estimate survival was found to be 36 months (95% CI = 14.30 - 57.69) in low-grade patients (n=19) and ten months (95% CI = 5.19 - 14.80) in high-grade patients (n=30) (p = 0.013). Stage (Stage I, n=12; Stage II, n=2; Stage III, n=10, and Stage IV, n=24) and having a higher stage (n=34) was not a significant factor affecting survival (p = 0.602, p = 0.366, respectively).

When the patients who had taken only surgical treatment (group I) (n=3), who had taken at least one or more CRHT methods besides surgery (group II) (n=15), who had taken

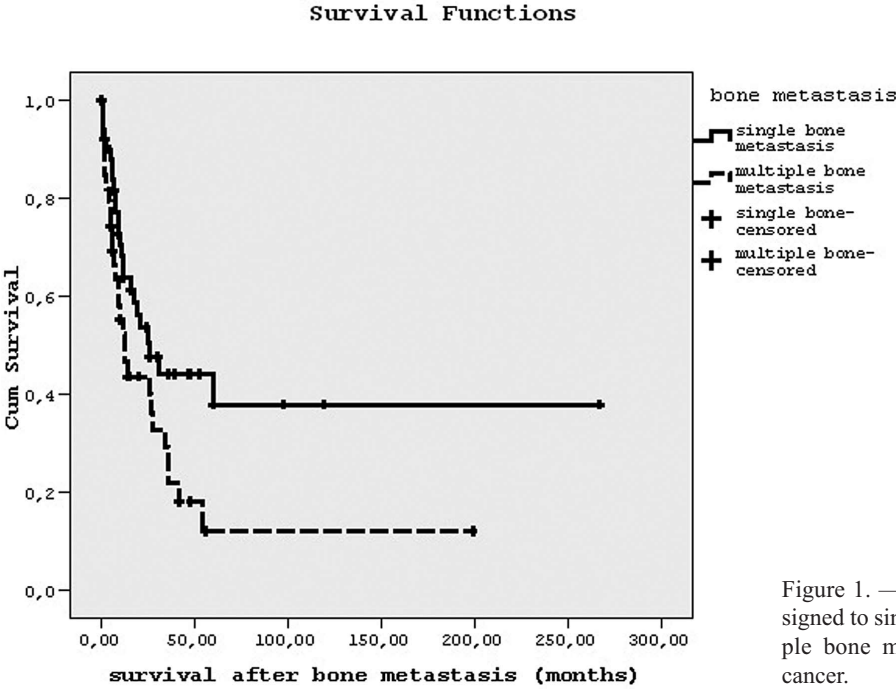

Figure 1. — Probability of survival for patients assigned to single bone metastasis (solid line) or multiple bone metastasis (broken line) in endometrial cancer.

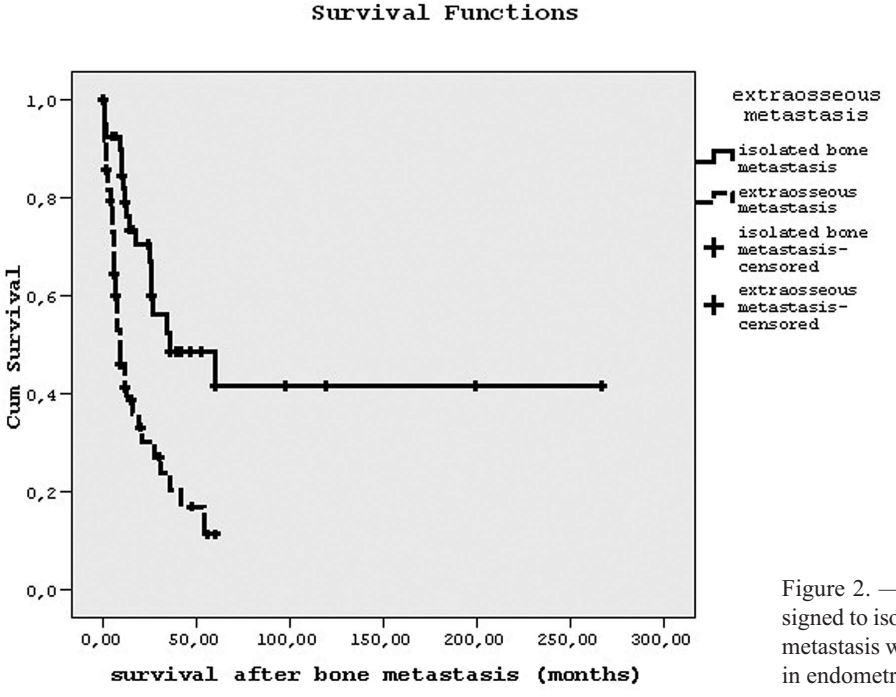

Figure 2. — Probability of survival for patients assigned to isolated bone metastasis (solid line) or bone metastasis with extraosseous metastasis (broken line) in endometrial cancer.

at least one or more of CRHT methods in combination without surgery (group III) (n=33), and who did not take any treatment (n=3) were evaluated by Kaplan-Meier analysis in order to assess the effect of the performed treatment on survival and median estimate survival was found to be 12 months (95% CI = 4.92 - 19.07) for group III and 36 months (95% CI = 18.97 - 53.02) for group II ($p < 0.001$) (Figure 3). Since the number of patients in group I and group IV were less for statistical analysis, median estimate survival could not be calculated for them.

When the patients who underwent the options of tumor curettage, bone resection or amputation for bone metasta-

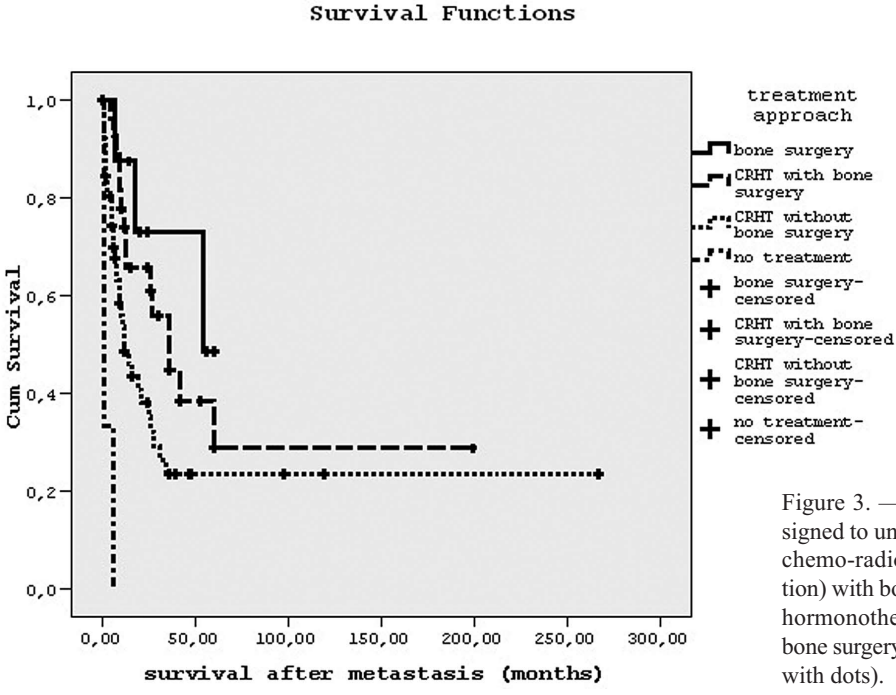

Figure 3. — Probability of survival for patients assigned to underwent only bone surgery (solid line) or chemo-radio-hormonotherapy (single or combination) with bone surgery (broken line) or chemo-radio-hormonotherapy (single or combination) without bone surgery (dotted line) or no treatment (dashed line with dots).

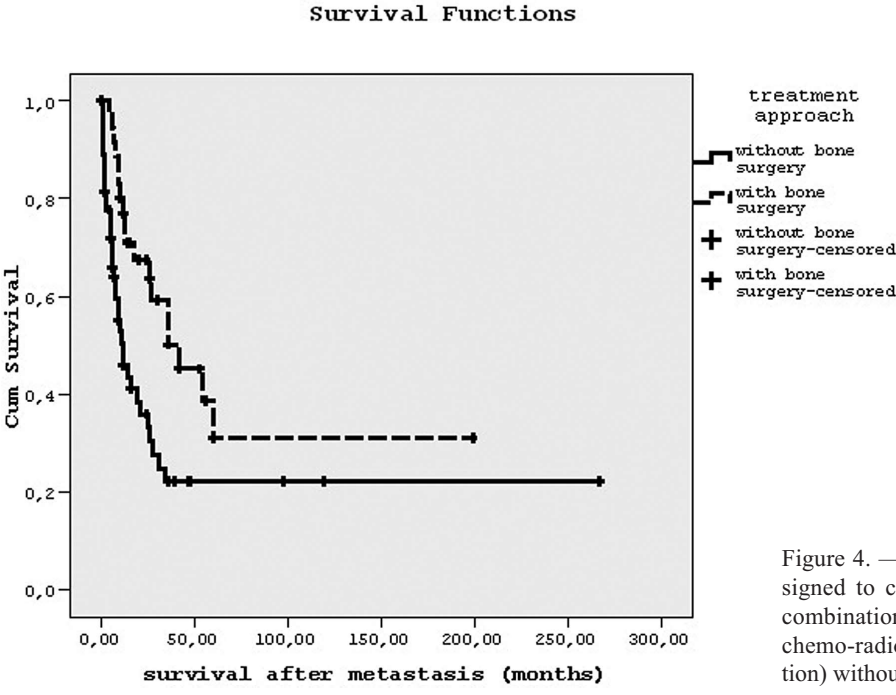

Figure 4. — Probability of survival for patients assigned to chemo-radio-hormonotherapy (single or combination) with bone surgery (broken line) or chemo-radio-hormonotherapy (single or combination) without bone surgery (solid line).

sis and patients who did not undergo surgery were evaluated by Kaplan-Meier test in order to assess the factors affecting survival and median estimate survival time was found to be 12 months (95% CI = 5.89 - 18.10) in patients who were not surgically treated (n=36) and it was found to be 42 months (95% CI = 16.58 - 67.41) in patients who underwent surgical treatment in addition to one or more of CHRT therapies (n=18) ($p = 0.006$) (Figure 4).

When Cox regression analysis was performed by the parameters, such as non-endometrioid histopathological type, having high grade, presence of multiple bone involvement, presence of extraosseous metastasis, and lack of surgery in

treatment method, it was found that statistically significant indicators affecting survival had a type II cancer (p = 0.012), presence of extraosseous metastasis (p = 0.002), and lack of surgery during treatment (p = 0.038). Presence of involvement in multiple bones and having a high grade were not found to be significant factors affecting survival (p = 0.310 and p = 0.422, respectively).

Discussion

Endometrial cancer rarely metastasis to bone in contrary to other solid tumors such as breast, lung, and renal cancers. Aalders *et al.* reported Stage IV endometrial cancer in 83 of 3,393 cases with cancer, bone metastasis in two cases (0.05%), and in their other study, 14 cases (3.69%) of bone metastasis out of 379 cases with recurrent endometrial adenocarcinoma [62, 63]. Similarly, in the study by Goff *et al.* on 927 endometrial cancer cases, 3% of patients had Stage IV disease and bone metastasis was present in only two patients (0.05%) [64]. In current studies on bone metastasis of endometrial cancer, Uccella *et al.* published the incidence of bone involvement of primary endometrial cancer as 0.8% in their study including the cases that were recognized by radiographic examinations but were not confirmed by histopathological examination [3]. However, Abdul-Karim *et al.* reported that they have detected bone metastasis in 25% of 67 cases with endometrial cancer in the light of premortem radiological findings and autopsy results [65].

Pain is the main complaint in the diagnosis of bone metastasis. Swelling and other inflammation symptoms may accompany pain, or complaints regarding nerve compression created by metastatic mass or obstruction findings may rarely be observed. In the present literature review, the authors found that bone-derived complaints were often misinterpreted as pain associated with trauma, arthritis, osteomyelitis, and plantar fasciitis even in patients who were known to have endometrial cancer previously. These patients have obtained a true diagnosis as a result of advanced assessments performed due to disease resistant to analgesic or antibiotic treatment. In the present review, a mean duration of 5.1 months has passed from the onset of complaints until the diagnosis of bone metastasis in 29 cases who provided enough data in order to calculate time. Certainly, CT, MRI and bone scan have a role besides direct graphies in true diagnosis of the disease during histopathological examination of bone biopsies. However, routine screening is not recommended for endometrial cancer patients in terms of bone metastasis [3, 66]. Interestingly, although it was reported in bone biopsy results of five cases, in which bone metastasis was detected first, that metastasis was derived from a malignancy with a gynecological origin, endometrial sampling was not performed due to lack of postmenopausal bleeding complaint and a duration of six to 36 months were lost until the detection of cancer in the uterus [6, 14, 42, 44, 60]. As a result, all kinds of bone and joint-derived pain may be associated with bone metastasis in patients diagnosed with cancer. Moreover, endometrial sampling must be performed in patients who were reported to have a malignancy with a gynecological origin following bone biopsy even in the absence of any complaint or ultrasonography finding.

Abdul-Karim *et al.* and Uccella *et al.* have reported that metastasis was present in axial skeleton (vertebra and hip) in 15 cases out of 17 and 17 cases out of 19, respectively, in whom they detected endometrial cancer bone metastasis which were mostly occurred in multiple bones [3, 65]. In the study with similar results by Kehoe *et al.*, most common metastasis area was vertebral column and pelvic bones in cases with recurrent cancer on bones; however, most common metastasis areas were lower extremity bones in the cases presented with bone metastasis (calcaneus, talus, tibia, femur, and fibula, respectively) [57]. When the cases presented with bone metastasis were reviewed in the literature, it was found that metastasis area was lower extremity bones in 80% [60]. This situation may be associated with early detection of extremity metastases since they cause more severe complaints. It is interesting that metastasis of endometrial cancer is detected on lower extremity bones in the opposite direction to lymphatic flow. The idea that these metastases have occurred as a result of the placement of tumor embolisms on lower extremity due to venous retrograde flow through valveless Batson's paravertebral venous plexus routes was widely accepted [9, 40, 56]. Also, another theory is that vascular invasion begins at the lymphatics from where tumor cells can reach venous return and joins systemic circulation by reaching arterial circulation from there [21].

Kehoe *et al.* have reported median time from the diagnosis of bone metastasis until death as ten months (26 months in isolated bone metastasis and eight months with multiple metastasis) and Uccella *et al.* have reported the median survival as 12 months (25 months in isolated bone metastasis) in their study [3, 56]. The most important prognostic factors were found to be as multiple bone involvement and the presence of extraosseous involvement (median survival was six months for each) in the case series of Uccella *et al.* in a statistically significant manner by dual group comparisons. The preset authors have observed that presence of extraosseous metastasis and multiple bone involvement significantly decreased survival. While median estimate survival was 26 months in single bone involvement, it decreased down to 13 months in the presence of multiple bone involvement. Median estimate survival of the patients without extraosseous metastasis decreased from 36 months to nine months in the presence of extra-abdominal metastasis. Overall survival time of the patients with Stage IV endometrial cancer was reported to be 21.3 months [67]. Considering that isolated bone metastasis was present in 46.1% of the cases in the present review, the authors suggest that prognosis of patients with only isolated bone metastasis without extraosseous in-

volvement is better than the other cases with Stage IV endometrial cancer.

It is well known that histological subtype of the tumor and grade III histology increase the probability of hematogenous metastasis in endometrial cancers [68]. In addition, the results of the studies analyzing the effect of histological subtype and grade on survival in Stage IV patients are controversial. In their study evaluating 47 cases with Stage IV endometrial cancer including two with bone metastasis, Goff *et al.* have reported that histological subtype, grade, stage, and metastasis area were not significant indicators in terms of prognosis (64). However, in the study by Tanioka *et al.* in which they evaluated 41 patients with Stage IV disease including three with bone metastasis, presence of grade I and II disease was one of the factors positively affecting survival (67). Uccella *et al.* indicated that histological type II disease was a significantly poor prognostic factor in their case series [3]. In the present literature review, having a cancer with a histological type II was the factor that was significantly affecting survival. Although the present authors have obtained a similar result, it is difficult to make an interpretation since the number of patients with a histological type II disease was few in this review. The relationship between survival and both histological subtype and grade in Stage IV patients with bone metastasis should be assessed by the studies with a higher number of patients.

The role of cytoreduction in patients with recurrent Stage IV endometrial cancer is still debatable. There is no any standard regimen identified for the treatment of the disease. In general, surgery, radiotherapy, chemotherapy, and hormonotherapy methods are used in combination considering the presence of any other metastasis areas, presence of different bone involvement areas, general condition of the patient, and patient's preferences in order to palliate or eliminate the pain or prolong survival [69]. While radiotherapy can successfully treat pain and invasion signs in extremity especially among patients with single bone involvement, chemotherapy and hormonotherapy positively contribute to survival in the presence of disseminated disease with multiple area involvement [70]. In case of clinical persistence in well-defined lesions, excision, resection or amputation may be evaluated as an option in the presence of pain irresponsive to radiotherapy or uncontrolled infection. It is suggested that most of the cases were benefited from combined aggressive therapy [19, 71]. Uccella *et al.* have evaluated the patients without extraosseous metastasis in their study and they have indicated that they did not see any significant advantage of only radiotherapy in the treatment of bone metastasis, surgery was not associated with a dramatic improvement in oncological outcomes, and hormonotherapy including megesterol in combination with other therapies was associated with better results [3]. In the present study, only the number of patients in the group that underwent surgery was less to allow statistical analysis. Therefore, whether they have taken CHRT or not, when the present authors assessed the patients who did and did not undergo surgery as two separate groups, they found survival in the patients who underwent surgery significantly better. Radiotherapy may be chosen for the palliation of pain in patients with poor life expectancy and surgical intervention may be considered for the patients with a higher life expectancy. The present authors do not forget that this condition may cause bias towards surgical intervention and they think that combination therapies including surgery have a positive effect on survival in the treatment bone metastases of endometrial cancers.

Limitations of this study were difficulties in finding sufficient data in quite old case reports and the doubts regarding that patients were adequately staged and evaluated by radiographic methods or not. Also, while 18 out of 21 patients were lost in one of two case series, other three were alive, and 16 out of 19 patients died in the other series. Only 15% of 40 cases were alive. Besides, 46% of the cases were alive in case reports. This condition is a clear indication of the tendency of case reports to publish data of patients with better outcomes and it is quite difficult to avoid this bias.

Conclusion

The first sign of endometrial cancers may be bone metastasis and associated pathological fracture. Bone metastasis should be considered in case of pain complaints that may be associated with the bone in all patients who were known to have endometrial cancer previously. Histological type of the tumor and presence of extraosseous involvement appear as important indicators of prognosis in patients with endometrial cancer with bone metastasis. There is available data regarding that patients with isolated bone metastasis have a better prognosis than the patients with stage IV endometrial cancer. Even treatment plan was performed by individualizing it for the patient by considering the factors such as general condition of the patient, patient's preferences, presence of single or multiple metastasis and the presence of extraosseous involvement areas, we believe that combination therapies including surgery will be appropriate for the treatment of bone metastasis although it is not supported by strong evidence.

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