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Treatment and prognosis of bone metastasis from cervical cancer (KCOG-G1202s)

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Abstract

Aim: The early and precise diagnosis and proper palliative treatment of bone metastasis is important for improving the quality of life of cervical cancer patients. The aim of this study was to clarify the clinical features, treatment modalities and prognosis of bone metastasis in cervical cancer patients in Japan.

Methods: The medical records of 75 cervical cancer patients with bone metastasis who were treated between January 2000 and December 2010 were retrospectively analyzed in a multi-institutional study.

Results: Fifty-four patients (72.0%) had a single bone metastasis. Bone metastases were found in the spine (46.7%) and pelvis (42.7%). Forty-three patients (57.3%) also had extra-osseous metastases. Most of the patients received radiotherapy, chemotherapy or both, but 25 patients (33.3%) received palliative care only. Bisphosphonates were given as palliative therapy to 25 patients (33.3%). The median overall survival after the diagnosis of bone metastasis was significantly shorter in patients with extra-osseous metastases than in those without extra-osseous metastases (14 vs 5 months; $P < 0.05$). The survival of patients who received chemotherapy following radiotherapy or concurrent chemoradiotherapy was significantly longer than that of the patients who received palliative care. On multivariate analysis, the presence of extra-osseous metastasis was an independent predictor of survival in patients with bone metastasis from cervical cancer.

Conclusions: Multidisciplinary treatment might improve the prognosis of patients with bone metastasis who do not have extra-osseous lesions.

Key words: bisphosphonates, bone metastasis, cervical cancer.

Introduction

Uterine cervical cancer, which is the third most commonly diagnosed cancer and the fourth leading cause of cancer-related death in women worldwide, accounted for 9% of new cancer diagnoses and 8% of the cancer deaths among women in 2008.[1] More than 85% of these cases and deaths occurred in developing countries. Uterine cervical cancer most commonly arises in the third to fifth decade of life.

Bone metastasis from cervical cancer occurs at the end of life in uterine cervical cancer patients; relapse and other organ cancer often occur during the course of treatment. After lung and liver, bone is the third most common site of distant metastasis.[2] Bone metastasis is considered to occur either from direct extension or as a hematogenous metastasis.[2]

The reported incidence of clinical bone metastasis in cervical cancer has ranged from 1.1% to 16%.[2–7] The metastasis rates differ greatly according method of

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detection. The rate of bone metastasis in living patients is lower than that reported in autopsy studies.[2,8]

The early and precise diagnosis and proper palliative treatment of bone metastasis is important for improving the quality of life of cancer patients. It is necessary to establish a multidisciplinary treatment approach, which includes surgery, radiotherapy and chemotherapy. Bone metastasis, however, is associated with poor prognosis, even when it is diagnosed early and the appropriate treatment is used. There are few published reports on bone metastasis in cervical cancer patients.[2,5,8,9] The aim of the present study was therefore to clarify the clinical features, treatment and prognosis of bone metastasis from cervical cancer in Japan.

Methods

The present study was designed as a multi-institutional retrospective study (Kansai Clinical Oncology Group: KCOG-G1202s trial). The patients enrolled in this study were diagnosed with bone metastasis from uterine cervical cancer between January 2000 and December 2010. This study was approved by the institutional review board of each institute. The subjects consisted of 75 patients who were diagnosed with bone metastasis from uterine cervical carcinoma and who underwent therapy at six hospitals in Japan (Kurume University Hospital, n = 24; Hyogo College of Medicine, n = 16; Tottori University Hospital, n = 9; Nagoya City University Hospital, n = 6; Oita University Hospital, n = 4; and Gifu University Hospital, n = 16).

The following data were collected from the patients' medical records: age at initial diagnosis; presence/absence of recurrence and bone metastasis; clinical and pathological stage (FIGO and TNM); presence/absence of extra-osseous metastasis; initial treatment modalities; treatment modalities used in patients with recurrence and bone metastasis; presence/absence of a residual tumor at the end of the initial treatment; symptoms; performance status; occurrence of fracture due to bone metastasis; site and number of bone metastases; size of the largest metastasis; prognosis; and cause of death. The overall survival time after bone metastasis was defined as the time from the diagnosis of bone metastasis until death or the last follow up.

Statistical analysis

JMP7 for SAS (SAS Institute, USA) was used for the statistical analysis. The overall survival times after bone metastasis were calculated using the Kaplan–Meier method and analyzed with log-rank test. Cox proportional hazards model was used to assess the impact of multiple covariates on the prognosis of bone metastasis from cervical cancer. Multivariate analysis is expressed as hazards ratio and 95%CI. $P < 0.05$ was considered to indicate statistical significance.

Results

Seventy-five patients were included in this retrospective analysis. Patient characteristics at the time of the diagnosis of cervical cancer are summarized in Table 1. The mean age was 52.2 years (range, 23–87 years). The histological types were as follows: squamous cell carcinoma, 77.3%; adenocarcinoma, 16.0%; adenosquamous carcinoma, 2.7%; and unknown, 4.0%). The clinical FIGO stages were as follows: stage I, n = 22 (29.3%); stage II, n = 18 (24.0%); stage III, n = 8 (10.7%) and stage IV, n = 26 (34.7%). Forty-four patients were found to have pelvic lymph node metastasis and 24 had distant metastasis (the site was bone, pulmonary or a lymph node other than the pelvic lymph node). Fifteen patients were found to have bone metastasis at the time of the initial diagnosis of cervical cancer. Nineteen patients had residual disease at the end of the initial treatment.

Table 1 Patient characteristics at initial diagnosis

Characteristics	n (%)
n	75
Age (years)	
Mean	52.2
Range	23–87
Histopathologic diagnoses	
Squamous cell carcinomas	58 (77.3)
Adenocarcinoma	12 (16.0)
Adenosquamous carcinoma	2 (2.7)
Unknown	3 (4.0)
FIGO stage	
I	22 (29.3)
II	18 (24.0)
III	8 (10.7)
IV	26 (34.7)
ND	1 (1.3)
Pelvic lymph node metastasis	
Positive	44 (58.7)
Negative	28 (37.3)
Unknown	3 (4.0)
Distant metastasis	
Bone	15(20.0)
Pulmonary	4(5.3)
Lymph node other than pelvis	15(20.0)

ND, not detectable.

The characteristics of these patients at the diagnosis of bone metastasis are summarized in Table 2. Thirty-five patients (46.7%) had bone metastasis within 12 months after the initial cancer diagnosis. Forty-seven (62.7%) had symptoms of bone metastasis. Fifty-four patients (72.0%) had a single bone metastasis; single bone metastasis occurred more frequently than multiple bone metastases. Bone metastasis was found in the spine (46.7%) and pelvis (42.7%); metastasis at other sites was found only in 12 patients (16.0%); 43 patients (57.3%) also had extra-osseous metastasis.

The treatments for the metastatic lesions are summarized in Table 3. Only two patients underwent surgical resection; it was not possible to eliminate all of the osseous lesions in either of these patients. Most patients received radiotherapy, chemotherapy or both. Twenty-five (33.3%) received palliative care only. Bisphosphonates (BP) were given as palliative therapy to 25 patients (33.3%).

Univariate analysis was carried out to identify prognostic factors (age, histopathology, duration after the initial cancer diagnosis, symptoms, number, size and site of metastasis, presence/absence of extra-osseous metastasis, and treatment modality) significantly associated with overall survival (OS; Table 4). Median OS after the diagnosis of bone metastasis was significantly longer in patients without extra-osseous metastasis than in patients with extra-osseous

Table 2 Patient characteristics at diagnosis of bone metastasis

Characteristics	n (%)
Age (years)	
Mean	54.3
Range	23–89
Duration after initial diagnosis (months)	
0	15 (20.0)
1–6	9 (12.0)
7–11	13(17.3)
≥12	35 (46.7)
Unknown	3 (4.0)
Symptom (pain)	
(+)	47 (62.7)
(−)	27 (36.0)
Unknown	1 (1.3)
No. bone metastases	
Single	54 (72.0)
Multiple	21 (28.0)
Maximum length	
<3 cm	30 (40.0)
≥3 cm	20 (26.7)
Unknown	25 (33.3)
Site of bone metastasis	
Spine	35 (46.7)
Pelvis	32 (42.7)
Other than pelvis and spine	12 (16.0)
Unknown	3 (4.0)
Extra-osseous metastasis	
(+)	43 (57.3)
(−)	32 (42.7)

Table 3 Treatment of bone metastasis

Modality	n (%)
Surgery + radiation + chemotherapy	2 (2.7)
Radiation only	16 (21.3)
Concurrent chemoradiotherapy	8 (10.7)
Radiation following the chemotherapy	8 (10.7)
Chemotherapy	16 (21.3)
Palliative care only	25 (33.3)
Bisphosphonate use	
(+)	25 (33.3)
(−)	50 (66.7)

Table 4 Univariate prognostic factors for overall survival

Factor	n	Median (months) (95% CI)	*P*
Age (years)			
<60	46	6 (4–11)	0.30
≥60	29	10 (3–23)	
Histopathology			
Squamous cell carcinomas	58	6 (4–11)	0.20
Adenocarcinoma oradenosquamous carcinoma	14	16 (4–24)	
Duration after initial diagnosis (months)			
0	14	4 (1–15)	0.64
≥1	58	7 (4–12)	
Symptoms			
(+)	47	6 (4–14)	0.38
(−)	27	8 (4–18)	
Number of bone metastases			
Single	54	6 (4–12)	0.92
Multiple	21	8 (1–22)	
Maximum length			
<3 cm	30	11 (6–20)	0.20
≥3 cm	20	4 (2–14)	
Sites of bone metastasis			
Pelvis only	27	8 (4–18)	0.69
Extra-pelvis ± pelvis	45	6 (3–12)	
Extra-osseous metastasis			
(+)	43	5 (3–10)	<0.05
(−)	32	14 (4–44)	
Treatment			
CCRT or RT following the chemotherapy	16	18 (4–22)	<0.05
Palliative care only	25	2 (1–5)	
Bisphosphonate use			
(+)	25	7 (4–16)	0.72
(−)	50	4 (2–11)	

CCRT, concurrent chemoradiotherapy; RT, radiotherapy.

metastasis (14 vs 5 months, $P < 0.05$, Fig. 1a). The OS of the patients who received chemotherapy following radiotherapy or concurrent chemoradiotherapy was longer than that of the patients who received palliative care only (18 vs 2 months, $P < 0.05$, Fig. 1b). Age, histopathology, duration after the initial cancer diagnosis, symptoms, number of bone metastases, size of the metastatic lesion, and the site of metastasis, however, were not statistically associated with prognosis.

On multivariate analysis to evaluate the prognostic factors associated with OS, the presence of extra-osseous metastasis was found to be an independent predictor of survival after bone metastasis (HR, 4.42; 95%CI: 2.12–10.04; $P < 0.05$, Table 5).

Discussion

The present multi-institutional study has some notable features with regard to the evaluation of the clinicopathological characteristics and the prognostic factors in patients with bone metastasis from cervical cancer. This study contains the largest multi-institutional cohort of patients with bone metastasis; this made it possible to compare the clinical characteristics and the prognostic factors in detail. Matsuyama *et al.* reported that metastasis to the bone occurred within 1 year in two-thirds of all patients.[5] Bone metastasis was detected within 1 year from the initial diagnosis of cervical cancer in approximately half of the present patients.

In the present study extra-osseous lesions were associated with a poorer prognosis than extra-osseous lesions in patients with bone metastasis. Okamura *et al.* reported that 39% of patients had extra-osseous metastasis.[6] In the present study, more patients had extra-osseous lesions. We speculated that the development of diagnostic modalities might have enabled the detection of smaller extra-osseous lesions. Yoon *et al.* reported that extra-osseous lesions were associated with a poorer prognosis in patients with bone metastasis from endometrial cancer.[10] In the present study, the same result was observed in cervical cancer.

The present results were consistent with many other reports in which the lumbar spine was the most frequent site of bone metastasis.[2,5,7] Although Thanapprapasar *et al.* reported that survival after the diagnosis of bone metastasis was longer in patients with pelvic bone metastasis compared than that in patients with extra-pelvic bone metastasis or both pelvic and extra-pelvic bone metastasis,[2] our results indicated that the metastatic site did not influence the survival.

Thanapprapasr *et al.* reported that most patients with bone metastasis had multiple metastases.[2] In contrast 72% of the present patients had single metastasis. We hypothesize that the advances in diagnostic techniques that have taken place in recent years, have led to an increase in earlier diagnosis. The survival of the patients with a single metastasis, however, did not differ from that in the patients with multiple metastases to a statistically significant extent, as it did in a previous report.[2]

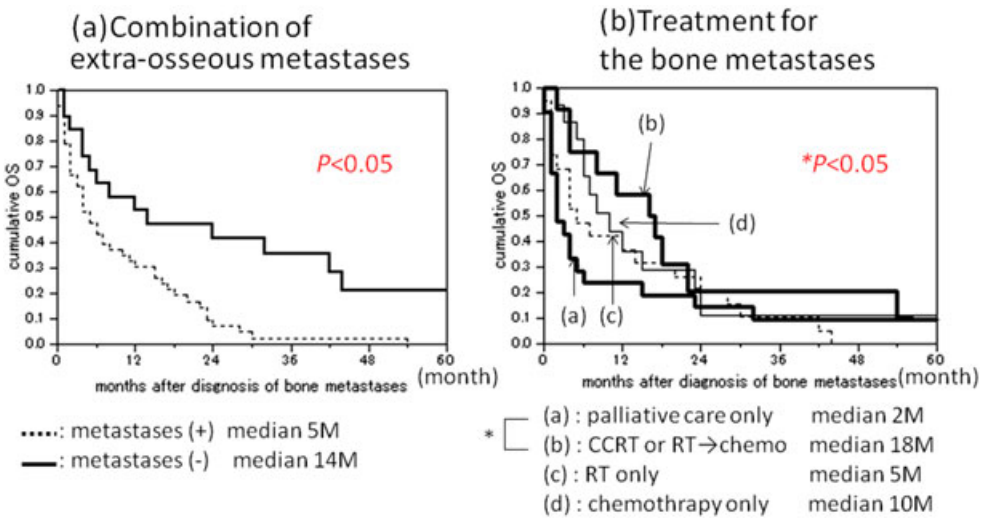

Figure 1 Overall survival (OS) after the diagnosis of bone metastasis according to (a) presence of extra-osseous metastasis and (b) treatment modality. (a) OS of patients (—) without extra-osseous metastasis (median, 14 months) was significantly longer than that of patients (····) with extra-osseous metastasis (median, 5 months). (b) A, palliative care only; B, concurrent chemoradiotherapy or radiotherapy following the chemotherapy; C, radiotherapy only; D, chemotherapy only. A vs B, $P < 0.05$.

Table 5 Multivariate prognostic factors for overall survival

Factor	Hazard ratio (95%CI)	*P*
Age (years)		
<60	1	
≥60	0.70 (0.37–1.31)	0.27
Histopathology		
Squamous cell carcinomas	1	
Adenocarcinoma or adenosquamous carcinoma	0.72 (0.30–1.66)	0.46
Duration after initial diagnosis (months)		
0	1	
≥1	1.04 (0.48–2.35)	0.91
Symptom		
(+)	1.04 (0.58–1.94)	0.90
(−)	1	
No. bone metastases		
Single	1	
Multiple	1.11 (0.55–2.15)	0.75
Sites of bone metastasis		
Pelvis only	1	
Extra-pelvis ± pelvis	1.06 (0.60–1.92)	0.84
Extra-osseous metastasis		
(+)	4.42 (2.12–10.04)	<0.05
(−)	1	
Treatment		
CCRT or RT following the chemotherapy	1	
Others†	2.12 (0.90–5.48)	0.08
Bisphosphonate use		
(+)	1	
(−)	1.63 (0.87–3.06)	0.12

†RT only/chemotherapy only/surgery/palliative care only. CCRT, concurrent chemoradiotherapy; RT, radiotherapy.

Although Thanapprapasr *et al.* and Yoon *et al.* reported that the patients with squamous cell carcinoma had longer overall survival than patients with non-squamous cell carcinoma,[2,11] we found no significant difference in the survival of the patients with these histological subtypes.

Yoon *et al.* reported that the OS of patients with bone metastasis at recurrence was significantly longer than that of patients with bone metastasis at the primary diagnosis in endometrial cancer,[10] but there was no significant difference in survival between recurrence and primary diagnosis in the present cervical cancer patients.

The treatments for bone metastasis include surgery, radiotherapy, or chemotherapy or a combination of these. In the present study, mean survival after the diagnosis of bone metastasis was 14.0 months, while the median survival was 6 months, which is similar to that in previous reports.[2,5,8] As previously reported, the combination of chemotherapy and radiotherapy was the most effective treatment.[5] In addition, radiotherapy provides effective pain relief (70%).[2,5] Bone metastasis, however, often occurs in or near areas that were the target of previous radiotherapy; thus the indications for radiotherapy should be carefully considered. It is difficult to determine the indications for surgery. In this study, only two patients were surgically treated and a complete resection was not possible in either patient.

In general, the presence of bone metastasis is considered to predict poor outcome in cervical cancer. Yoon *et al.* reported that survival after bone metastasis was longer in the patients who received radiotherapy (with/without chemotherapy) than in the patients who received chemotherapy alone as a salvage therapy.[11] We noted the same result on univariate analysis in the present study, but this was not statistically significant on multivariate analysis. This discrepancy might exist because radiotherapy is performed for both curative and palliative purposes. These results, however, suggest that a combination of chemotherapy and radiation might improve the OS of patients with bone metastasis in patients who do not have extra-osseous lesions.

In recent years, BP have been found to have antitumor effects through several mechanisms,[12–14] and in other types of cancer (e.g. prostate, lung and breast cancer) BP hves been shown to improve progression-free interval and prognosis.[15–20] Tsubamoto *et al.* also reported that the combination of chemotherapy with BP might be useful for controlling bone metastasis in patients with cervical cancer.[21] In the present study, it was not possible to show the efficacy of BP, which has previously been reported in patients with bone metastasis from other types of cancer. The present study, however, was a retrospective study in which BP were given to a limited number of patients; thus a further prospective study should be performed to determine the usefulness of BP therapy.

In conclusion, a multidisciplinary treatment approach might improve the prognosis of patients with bone metastasis who do not have extra-osseous lesions; and patients with extra-osseous lesions should be referred for palliative treatment.

Disclosure

The authors declare no conflicts of interest.

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