Clinicopathologic Features and Clinical Outcomes of Gastric Cancer Patients with Bone Metastasis

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(Received October 10, 2014; Accepted October 24, 2014)

Objective: We conducted a retrospective analysis to evaluate the clinical manifestations and outcomes of a population of gastric cancer patients with bone metastasis.
Methods: The subjects were 31 gastric cancer patients who were diagnosed with bone metastasis between January 2000 and December 2010.
Results: The overall median survival time (MST) was 100 days. The results of a multivariate analysis in relation to overall survival showed that the absence of extraosseous metastasis and having received chemotherapy were favorable prognostic factors. MST was 269 days in the bone metastasis alone group (n = 6) and 65 days in the extraosseous metastasis group (n = 25). We divided the extraosseous metastasis group into two subgroups according to whether the patient had received chemotherapy. Evaluation of the response in the chemotherapy group showed that the subgroup of patients with progressive disease had a significantly longer MST than the no-chemotherapy group (63 days vs. 21 days, $p = 0.012$).
Conclusions: We concluded that it is useful to divide gastric cancer patients with bone metastasis into two groups according to whether they have extraosseous metastasis. Aggressive chemotherapy should be considered as a means of improving the prognosis of gastric cancer patients with extraosseous metastasis.

Key words: Bone metastasis, Clinical outcome, Clinicopathologic feature, Gastric cancer, Prognostic factor

INTRODUCTION

Breast cancer, prostate cancer, lung cancer, and kidney cancer are associated with particularly high rates of metastasis to bone [1]. Bone metastasis by gastric cancer is rare, occurring in only 0.9–2.1% of gastric cancer patients [2, 3]. Since the incidence of gastric cancer is higher in Japan than in Western countries [4], bone metastasis by gastric cancer occupies a more important position clinically in Japan.

The outcome of gastric cancer with bone metastasis is poor, and median survival times (MSTs) of 3–4 months after the detection of bone metastasis have been reported in some studies [5, 6]. Since bone metastasis in gastric cancer patients results in poor performance status because it causes intractable pain, appropriate treatment strategies for such patients are needed, but the treatment options remain limited. Moreover, because of the relatively small size of the subset of gastric cancer patients who have bone metastasis, no systematic attempts have ever been made to determine the optimal treatment. In the present study we retrospectively attempted to identify the clinicopathologic features, treatment outcome, and prognostic factors for survival of gastric cancer patients with bone metastasis.

PATIENTS AND METHODS

Between January 2000 and December 2010, a total of 1837 gastric cancer patients were treated in the Department of Gastroenterological Surgery of Tokai University Hospital, and 31 (1.7%) of them were found to have bone metastasis. Bone metastasis was diagnosed by examining patients whenever bone metastasis was suspected because of a bone-related symptom, such as localized pain, paralysis, or a movement disorder, had developed or the patient's serum alkaline phosphatase (ALP) value was found to be elevated. The diagnostic imaging modalities used to identify bone metastases included radionuclide bone scintigraphy, plain radiography, computed tomography, and magnetic resonance imaging. The median follow-up period after the diagnosis of bone metastasis was 100 days (range: 9–529 days).

We retrospectively reviewed the patients' records and analyzed the following clinical data: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, 7th UICC TNM stage, symptoms, location of bone metastases, extraosseous metastases, interval between the diagnosis of gastric cancer and detection of bone involvement, and laboratory findings, including the carcinoembryonic antigen (CEA), carbohydrate antigen (CA19–9), and serum ALP values. The histological diagnostic criteria were based on the Japanese histologic classification [7]. The histological types of the Japanese classification, i.e., differentiated carcinoma and undifferentiated gastric carcinoma corresponded to adenocarcinoma and poorly cohesive carcinoma, respectively, in the current WHO classification [8]. Patients with other pathological subtypes of gastric cancer (small cell, neuroendocrine, squamous cell carcinoma, lymphoma)

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and patients with a coexisting second primary cancer were excluded. The investigation conformed to the principles outlined in the Declaration of Helsinki. This retrospective study was approved by the Institutional Review Board (IRB) of the Tokai University Hospital.

Statistical analysis

The χ^2 test was used to compare categorical data, and the Mann-Whitney *U* test or Kruskal-Wallis *H* test was used to compare continuous variables. Mean values were compared by the *t*-test. The primary endpoint of the study was overall survival, defined as the period from the date of diagnosis of bone metastasis to the date of death from any cause. Overall survival was estimated by the Kaplan-Meier product-limit method, and the survival curves of different groups were compared by using the log-rank test. Multivariate analysis was performed by using a Cox proportional hazards model. All *p* values were two-sided, and *p* values < 0.05 were considered statically significant. The SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) software program was used for all statistical analyses.

RESULTS

Patient characteristics

The median age of the 31 patients at the diagnosis of bone metastasis was 62 years (range: 44−77 years), and they consisted of 23 males and 8 females. The histological type of the cancer according to the Japanese classification was the differentiated type in 10 patients and the undifferentiated type in 21 patients. The disease stage at the time of the diagnosis of gastric cancer was Stage I in 2 patients, Stage II in 3 patients, Stage III in 9 patients, and Stage IV in 17 patients (Table 1). The lymph node metastasis classification in the 20 patients whose initial treatment was surgery was: N0 in 2 patients; N1 in 1 patient; N2 in 1 patient; and N3 in 16 patients.

The bone metastasis was synchronous in 8 patients and metachronous in 23 patients. The median interval before the diagnosis of metachronous bone metastasis was 308 days (13−2505 days). The bone metastasis was solitary in 6 patients and multiple in 25 patients, and the sites of the bone metastases were the spine (n = 29), pelvis (n = 15), and ribs (n = 14). In 6 patients (19.4%) the metastasis was limited to bone, and in the other 25 patients there was metastasis to at least one other organ besides bone. The most common sites of extraosseous metastasis were distant lymph nodes (n = 20), peritoneum (n = 13), liver (n = 8), and lung (n = 5). The initial symptoms of bone metastasis were local or generalized bone pain (n = 17), neurological symptoms (n = 2), and both pain and neurological symptoms (n = 2), and 10 (32.3%) patients were asymptomatic. ECOG performance status was 0−1 in 18 patients and 2−4 in 13 patients. None of the patients developed pathological fractures or hypercalcemia. Disseminated intravascular coagulation occurred in 6 patients. At the time bone metastasis was diagnosed 22 patients had an elevated serum CEA value, 18 had an elevated serum CA19-9 value, and 26 had an elevated serum ALP value, and their respective median values were 13.3 ng/ml (range: 0.5−3121.6), 65.4 U/ml (range: 1.0−189244.2), and 682.0 IU/l (range: 190.0−4160.0).

Table 1 Patients characteristics

	Patients
Median age, years	62 (44 ~ 77)
Sex	
Male	23
Female	8
Location	
Upper1/3	10
Middle1/3	9
Lower1/3	6
Whole stomach	6
Gross type	
Circumscribed	9
Infiltrative	22
Histologic type	
Differentiated	10
Undifferentiated	21
TNM stage	
Ⅰ	2
Ⅱ	3
Ⅲ	9
Ⅳ	17
Treatment for primary tumor	
Surgery	20
Chemotherapy	9
Best supportive care	2

Treatment after the diagnosis of bone metastasis consisted of chemotherapy in 18 patients (58.1%), radiotherapy in 4 patients, and only best supportive care (BSC) in 9 patients. The chemotherapy regimen was S-1-based in 9 patients, 5-fluorouracil combined with cisplatin in 3 patients, taxotere monotherapy in 1 patient, irinotecan monotherapy in 1 patient, and other regimens in 4 patients. Second-line chemotherapy was performed in only 2 of the 18 patients.

Prognostic factor analysis

The 1-year survival rate after the diagnosis of bone metastasis was 9.7%, and MST was 100 days. To identify prognostic factors for survival in the patients with bone metastasis we performed a univariate analysis in relation to overall survival for the factors age, ECOG performance status, pattern of bone metastasis presentation (synchronous or metachronous), presence of distant metastasis at sites in addition to bone, number of bone metastases, treatment method (chemotherapy or no chemotherapy), etc (Table 2). Absence of extraosseous metastasis ($p = 0.006$) was identified as a factor significantly associated with a better outcome. Clinical parameters with a *p* value < 0.10, i.e., age, extraosseous metastasis, and chemotherapy, were included in the multivariate analysis. Using the Cox proportional hazards model resulted in identification of absence of extraosseous metastasis (relative risk [RR] 10.158; $p = 0.000$; 95% confidence interval [CI] 2.999-34.408) and having received chemotherapy (RR 4.752; $p = 0.001$; 95% CI 1.889-11.955) as significant favorable prognostic factors (Table 3). We did not divide the

Table 2 Univariate analysis of prognostic factors for overall survival in all patients

Variables	Patients	RR	95%CI	*p* value
Age				
< 65	16	1.908	0.898–4.054	0.093
≥ 65	15			
Sex				
Male	23	1.133	0.499–2.570	0.765
Female	8			
ECOG performance status				
0 ~ 1	18	1.670	0.789–3.536	0.180
2 ~ 4	13			
Gross type				
Circumscribed	9	1.209	0.547–2.672	0.640
Infiltrative	22			
Histologic type				
Differentiated	10	1.340	0.611–2.941	0.465
Undifferentiated	21			
TNM stage				
Ⅰ ~ Ⅲ	14	1.487	0.716–3.089	0.288
Ⅳ	17			
Pattern of bone metastssis				
Synchronous	8	1.008	0.427–2.376	0.986
Metachronous	23			
Bone involvement				
Solitary	6	1.396	0.562–3.466	0.472
Multiple	25			
Symptom				
Absent	10	1.272	0.577–2.802	0.551
Present	21			
ALP				
< 600	14	1.107	0.537–2.280	0.783
≥ 600	17			
CEA				
< 13	15	1.303	0.665–2.552	0.441
≥ 13	16			
Extraosseous metastasis				
Absence	6	4.174	1.518–11.474	0.006
Presence	25			
Chemotherapy				
(–)	13	1.943	0.918–4.113	0.082
(+)	18			

ALP = serum alkaline phosphatase; CEA = serum carcinoembryonic antigen; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; RR = relative risk.

Table 3 Multivariate analysis of prognostic factors for overall survival in all patients

Variables	Patients	RR	95%CI	*p* value
Age				
< 65	16	2.227	0.963–5.152	0.061
≥ 65	15			
Extraosseous metastasis				
Absence	6	10.158	2.999–34.408	0.000
Presence	25			
Chemotherapy				
(–)	13	4.752	1.889–11.955	0.001
(+)	18			

CI = confidence interval; RR = relative risk.

patients as a whole into groups according to whether they had these prognostic factors, because there were only 6 patients with bone metastasis alone. In the bone metastasis alone group (n = 6), the 1-year survival rate was 33.3%, and the MST was 269 days, as opposed to 4.0% and 65 days, respectively, in the extraosseous metastasis group (n = 25), and the differences in both parameters were statistically significant ($p = 0.003$ and $p = 0.003$, respectively) (Fig. 1).

Based on the results of the multivariate analysis, we divided the bone metastasis plus extraosseous metastasis group into two subgroups: a group of 15 patients who had received chemotherapy and a group of 10 patients who had not received chemotherapy. MST was significantly longer in the chemotherapy group than in the no-chemotherapy group (125 days vs. 21 days, $p = 0.001$) (Fig. 2). The results of the evaluation of response in the chemotherapy group revealed a partial response (PR) or stable disease (SD) in 5 patients and progressive disease (PD) in 10 patients. MST was 138 days in the PR and SD group and 63 days in the PD group. The MST of the PD group was significantly longer than in the no-chemotherapy group (63 days vs. 21 days, $p = 0.012$).

DISCUSSION

Since bone metastasis in gastric cancer patients usually causes intractable pain and has been associated with a poor prognosis, it is clinically important to understand the clinicopathologic features of gastric cancer with bone metastasis. According to macroscopic type the gastric cancers that metastasize to bone tend to be the infiltrative type, and the cancers tend to be undifferentiated adenocarcinomas according to the Japanese classification. Gastric cancer patients with bone metastasis tend to have advanced-stage disease and lymph node metastasis [6, 9, 10], and the majority of the patients in the present study had the infiltrative type macroscopically, the undifferentiated type according to the Japanese classification histologically, N3 lymph node metastasis, and Stage III or Stage IV disease.

Ahn *et al.* [6] reported an MST of gastric cancer patients with bone metastasis of 3.0 months, and Lee *et al.* [5] reported an MST of 4.0 months. The MST in the present study was 100 days. Park *et al.* [11] attempted to identify prognostic factors in gastric cancer patients with bone metastasis and reported finding that performance status, number of bone metastases, and serum CEA values were significant prognostic factors for survival. Kim *et al.* [12] conducted a similar study and reported identifying serum sodium values, lung metastasis, and peritoneal dissemination as prognostic factors. The multivariate analyses in the present study revealed significant differences in survival according to whether extraosseous metastasis was present and whether chemotherapy had been performed. The identification of chemotherapy as a favorable prognostic factor was consistent with the results of Kwon's study [13]. There have been few reports that extraosseous metastasis was identified as a significant prognostic factor for survival in gastric cancer patients with bone metastasis. Kammori *et al.* [14] reported the case of a patient with recurrence in the form of bone metastasis alone after surgery for gastric cancer and achievement of a 13-month survival time. Saito *et al.* [15] reported a similar case, and they achieved a 24-month survival time. Toyoda *et al.* [16] reported finding that the absence of extraosseous metastasis was an independent predictor of longer survival in renal cancer patients with bone metastasis. Orita *et al.* [17] identified the absence of extraosseous metastasis as an independent favorable prognostic factor in a study of thyroid cancer patients with bone metastasis. Absence of extraosseous metastasis has been identified as an independent prognostic factor for solid tumors at other sites, and that finding is consistent with the results of the present study. Since the prognosis of gastric cancer patients with bone metastasis differs according to whether metastasis to other organs has been detected, classifying patients into two groups according to whether they had extraosseous metastasis appeared to be useful.

When we divided the patients as a whole into two groups according to whether extraosseous metastasis was also present, there were 6 patients in the bone metastasis alone group and 25 in the bone metastasis plus extraosseous metastasis group. Because of the small number of patients in the bone metastasis alone group we did not divide it into two groups according to treatment method. Division of the bone metastasis plus extraosseous metastasis group into two groups according to treatment method revealed a significantly longer MST in the chemotherapy group than in the no-chemotherapy group, and the subgroup of patients with PD in the chemotherapy group had a significantly longer MST than the no-chemotherapy group. We conducted a similar analysis of the patients with an ECOG performance status of 2 or less in the bone plus extraosseous metastasis group to eliminate the effect of ECOG performance status on the results of chemotherapy (data not shown). The PD subgroup of the chemotherapy group had a significantly longer MST than the no-chemotherapy group (70 days vs. 28 days, $p = 0.049$). The results of our study suggest that aggressively performing chemotherapy is necessary to improve the prognosis of gastric cancer patients with metastasis to another site in addition to bone.

The Japanese Gastric Cancer Treatment Guidelines recommend S-1 combined with cisplatin as the first-line chemotherapy regimen for progressive or recurrent gastric cancer [18], and the chemotherapy regimens of many of the patients in the present study were S-1-based. Park *et al.* [11] used a variety of combination chemotherapy regimens, including taxane-based regimens, anthracycline-based regimens, and irinotecan-based regimens, to treat the majority of gastric cancer patients with bone metastasis. Since no prospective studies of therapeutic regimens in gastric cancer patients with bone metastasis have ever been conducted in Japan or abroad, the optimal chemotherapy regimen remains unknown.

In conclusion, the outcome of the gastric cancer patients with bone metastasis in this study was poor. However, because based on the results of the multivariate analysis the survival time of patients with bone metastasis alone was longer, it appeared useful to classify gastric cancer patients with bone metastasis into 2

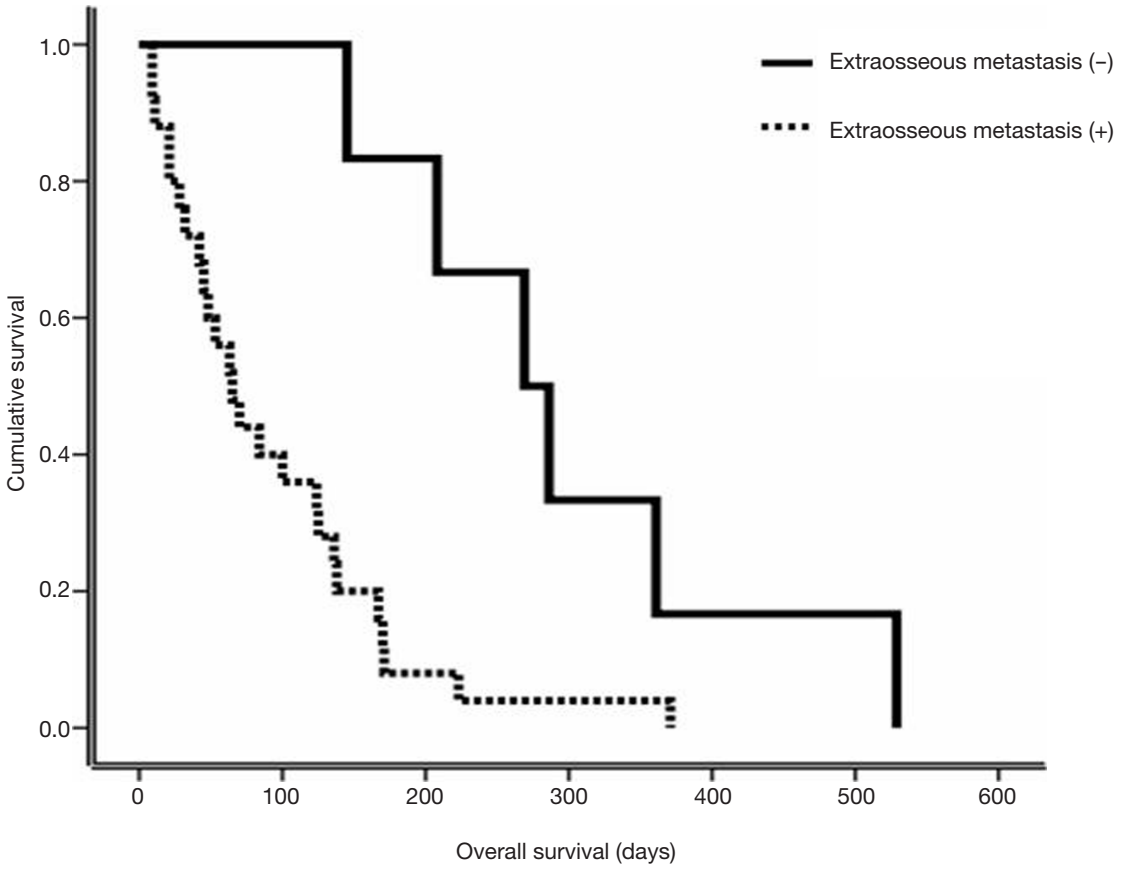

Fig. 1 Overall survival according to the status of extraosseous metastasis for all patients. Group extraosseous metastasis (−), patients with bone metastasis alone; group extraosseous metastasis (+), patients with metastasis to another site in addition to bone.

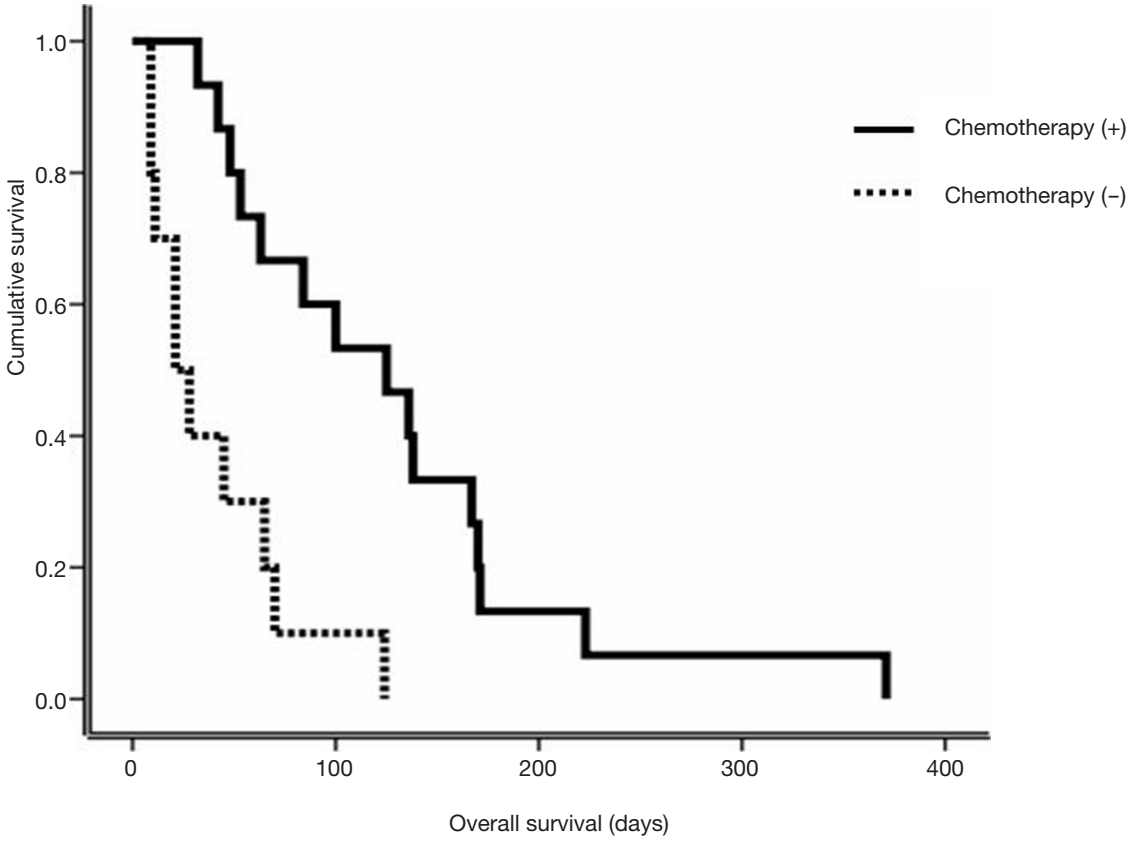

Fig. 2 Overall survival according to treatment method in extraosseous metastasis group. Group chemotherapy (+), patients received chemotherapy; group chemotherapy (−), patients received no chemotherapy.

groups according to whether they have extraosseous metastasis. Since the subgroup of patients with PD in the group of patients with extraosseous metastasis who had received chemotherapy had a significantly longer MST than the group that had not received chemotherapy, aggressively performing chemotherapy should be considered as a means of improve the prognosis of gastric cancer patients with metastasis to another site in addition to bone.

CONFLICT OF INTEREST

Kenji Nakamura, Mifuji Tomioku, Kazuhito Nabeshima, Seiei Yasuda declare that have no conflict of interest.

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