Clinical Pattern and Outcome of Gastric Cancer Patients with Skeletal Metastases

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Clinical Pattern and Outcome of Gastric Cancer Patients with Skeletal Metastases

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The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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또한 지금까지 살아온 30년 동안 항상 옆에서 지켜봐 주시고, 든든한 후원자가 되어 주셨던 부모님께 정말 감사 드리며, 지금 공부하느라 고생이 많은 동생, 영순이에게도 고맙다는 말을 전하고

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지면을 통해서 일일이 언급을 하지 못했지만 그동안 저를 아끼고 사랑해주신 모든 분들께 다시 한번 진심으로 감사 드립니다.

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ABSTRACT

Clinical pattern and outcome of gastric cancer patients with skeletal metastases

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BACKGROUND: Skeletal metastasis is an adverse prognostic factor in gastric cancer, with a rapidly deteriorating clinical course and quality of life. However, current data provide only limited information about it. Herein we evaluated the clinical manifestations and prognostic factors, and treatment outcomes of gastric cancer patients with skeletal metastasis at diagnosis or during treatment.

METHODS: We retrospectively reviewed the patients treated between January 1998 and May 2008 in Yonsei University Health System. Radiographs of specific bones were taken to diagnose skeletal metastases after an abnormal bone scan or because of clinical symptoms such as pain or paralysis. Radiologists who had no knowledge of the results of any other radiologic or biochemical examinations interpreted the radiographs.

RESULTS: We identified skeletal metastasis in 203 (2.4%) of 8,633 patients; 126 patients (62%) had skeletal metastasis at diagnosis (synchronous), and remaining 77 patients developed metastasis during follow-up (metachronous).

The median time to skeletal metastasis was 16 months (range, 4 to 87 months). Most patients (n=180, 89%) demonstrated metastasis involving multiple bones and the spine (86%) was most frequent site. Six patients (3%) developed skeletal metastasis-related events (SRE): Three suffered pathologic fractures, one developed paralysis, and two developed hypercalcemia.

As for treatment, 120 patients (59%) received chemotherapy, with or without radiotherapy, and remaining 83 received local (radio)therapy or supportive care only. The median survival time after skeletal metastasis was 103 days (95% CI, 80-126 days).

Multivariate analysis revealed that elevated ALP [> 158 IU/L; Relative risk (RR)=2.00, $p<0.001$] and poor performance status [ECOG 3-4; RR=2.11, $p=0.003$] implied a poor prognosis. For patients who had none or only one of these adverse factors identified, chemotherapy had a beneficial effect ($p<0.0001$).

CONCLUSION: This is the first study to investigate the factors that predict survival in gastric cancer patients with skeletal metastasis. We recommend that therapy for gastric cancer with skeletal metastasis be tailored to the adverse factors of each patient in order to extend survival and improve the quality of life

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Key words : stomach cancer, skeletal metastasis, prognostic factor

Clinical Pattern and Outcome of Gastric Cancer Patients with Skeletal metastases

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I. INTRODUCTION

Gastric cancer remains the second most common cause of cancer deaths despite a declining incidence in many developed countries[1]. Despite early diagnosis, radical surgery and adjuvant chemotherapy, the five-year survival rate remains stable at about 50%. Curative treatment of gastric cancer requires complete elimination of cancer cells, and only radical dissection can demonstrably achieve this goal. Even after apparently curative resection, however, one-half of patients experience recurrence at regional and/or distant sites, and death from gastric cancer almost always results from recurrence with metastasis.

Metastatic gastric cancer is a therapeutic challenge for oncologists. Metastasis occurs in various forms or at more than one site simultaneously. Patterns of metastasis differ between Asian and Western populations, with

peritoneal metastasis most commonly reported in Asian studies and hematologic spread in the West[4]. Outside the lymphatic system, lung and liver predominate among metastasis sites. To date, however, skeletal metastasis is not well characterized. The incidence of skeletal metastasis is uncertain, and may be under- or over-estimated. Radiological examination for detection of skeletal metastasis is not a routine practice and international guidelines rarely refer to it at diagnosis or during treatment.

Skeletal metastasis from solid tumors of the breast, prostate, lung, and kidney indicate a rapidly deteriorating clinical course that is refractory to conventional treatment. Pathologic fractures and sudden paralysis occurs sometimes because of spinal metastasis. Pain and hematologic disorders, which are associated with skeletal metastasis, may markedly reduce the quality of life. Also in gastric cancer, a recent study shows that skeletal metastasis independently predicts poor survival. However, skeletal metastasis from gastric cancer has not been extensively investigated. Only a few small studies are available yet.

Herein, we retrospectively evaluated the clinicopathological menifestations, treatment outcomes and prognostic factors in gastric cancer patients who had skeletal metastasis at diagnosis or during treatment. In addition, we attempted to identify a subgroup of patients who would benefit from systemic treatment.

II. PATIENTS AND METHODS

1. Patient selection

We reviewed medical records of 8,633 patients of gastric cancer treated at Severance Hospital, Yonsei Health System between January 1998 and May 2008. The criteria for inclusion for this study were as follows: (1) age ≥ 18; (2) histologically confirmed adenocarcinoma of stomach; and (3) confirmed skeletal metastasis present at diagnosis (synchronous metastasis) or newly developed during follow-up (metachronous metastasis). Patients of the gastro-esophageal junction cancer and double primary cancer were excluded.

2. Patient evaluation

Pretreatment evaluation of all the patients included chest radiography, computed tomography (CT) of abdomen–pelvis, radionuclide bone scan, serum tumor markers (CEA, CA19-9), and esophagogastroduodenoscopy. Recently, we have used ^{18}F FDG-PET scan for screening of distant metastasis. For gastrectomized patients, at the end of the planned adjuvant therapy, a follow-up study was carried out with chest radiography, computed tomography (CT) of abdomen–pelvis, radionuclide bone scan, and esophagogastroduodenoscopy. These patients were followed up for the first 2 years, every 6 months until the tenth year, and then every year thereafter. For patients not receiving gastrectomy (including stage IV patients), imaging studies for tumor

measurement and serum biochemistry (including tumor markers) were conducted every 2-3 cycles of chemotherapy. Imaging study included the CT scan of involved anatomical lesion. Radionuclide bone scan was done for patients with initial bone metastasis and with newly developed bone-related symptoms such as localized (generalized) pain, paralysis or movement disorders.

3. Diagnosis of skeletal metastasis

Radiography tools for identifying skeletal metastasis included radionuclide bone scan (whole body bone scan), plain radiography of bones, computed tomography (CT), and magnetic resonance imaging (MRI). To confirm an individual lesion as a skeletal metastasis, we reviewed all available correlative radiographic studies. Bone scans were obtained four hours after intravenous injection of ^{99m}Tc-labeled methyldiphosphonate and were recorded using a gamma camera. Hot or cold lesions seen on bone scans were considered significant only if supported by radiographic evidence of metastasis by other radiographs; Simple radiography, CT or MRI of a specific bone were taken to document abnormal findings on a bone scan or clinical symptoms such as pain, motion difficulty or paralysis compatible with skeletal metastasis. Radiologists who had no knowledge of the results of any other clinical or biochemical examinations interpreted the radiographs. If an FDG-PET scan showed abnormal uptake, bone scan and radiographs were done to confirm skeletal

metastasis.

4. Data accrual

From medical records and pathology reports, we accrued the basic clinic-pathologic parameters: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, signs and symptoms at presentation and at diagnosis of skeletal metastasis, histology, size, and location of tumor, number and extent of lymph node metastasis, initial stage of cancer.

Skeletal metastasis-related parameters included time from gastric cancer diagnosis to bone involvement, site and number, combined metastasis, presence of and time to skeletal metastasis-related events (SRE), and laboratory findings of tumor markers; carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19-9), lactate dehydrogenase (LDH), and serum alkaline phosphatase (ALP).

5. Statistical analysis

The primary endpoint of the study was overall survival (OS), defined from the date of bone metastasis to the date of death from any cause. The OS was estimated using the Kaplan-Meier product-limited method, and survival curves were compared between groups using the log-rank test.

Laboratory data were initially recorded as continuous variables and later dichotomized according to the median value of each variable. In the univariate analyses, the following factors were included: age, sex, performance status,

tumor histology, patterns of bone metastasis, metastasis to other organs (peritoneum, liver, distant lymph node, lung, and ovary), tumor markers (CEA, CA 19-9, ALP) and treatment modality. Multivariate analysis was performed using Cox proportional hazard regression model. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

III. RESULTS

1. Patient characteristics

In total, 8,633 patients, 7,507 patients received gastrectomy either curative or palliative, and 69 patients (0.9%) of these developed bone metastasis during follow-up. Remaining 1,126 patients were diagnosed with distant metastasis. Among them 8 patients developed new skeletal metastasis during chemotherapy. Thus the 77 patients comprised metachronous metastasis. One-hundred twenty-six patients (11.2%) demonstrated skeletal metastasis at diagnosis, who comprised synchronous metastasis. Therefore, 203 patients were included in the analysis.

The baseline characteristics of the patients are presented in **Table 1**. For synchronous metastasis, the median age was 52 years (range, 24-83), and 71 (56%) patients were men. A large proportion of these tumors was Bormann type 3, and histologically, poorly differentiated or signet ring cell predominated.

For the metachronous group, median age was 51 years (range, 28-71). 59 patients received curative resection. The median interval from the diagnosis of gastric cancer to skeletal metastasis was 16 months (range, 4 - 87 months). Male predominance and histopathological findings were similar to those of synchronous group. The majority of patients had a good performance status.

Table 1. Patient characteristics

		Synchronous (n= 126) (%)	Metachronous (n= 77) (%)	Total (n= 203) (%)
Median age, years [range]		52 [24-83]	51 [28-71]	51 [24-83]
Sex	Male	71 (56%)	46 (60%)	117 (57%)
	Female	55 (44%)	31 (40%)	86 (43%)
Performance status	0-1	99 (79%)	67 (87%)	166 (82%)
	2-4	27 (21%)	10 (13%)	37 (18%)
Histology	WD-MD	25 (20%)	13 (17%)	38 (20%)
	PD-SRC	91 (72%)	56 (73%)	147 (72%)
	Unknown	10 (8%)	8 (10%)	16 (8%)
Gross type	EGC	9 (8%)	3 (4%)	12 (6%)
	Type 1	3 (2%)	0 (0%)	3 (2%)
	Type 2	13 (10%)	10 (13%)	23 (11%)
	Type 3	63 (50%)	40 (51%)	103 (51%)
	Type 4	19 (15%)	19 (25%)	38 (19%)
	Unclassified	19 (15%)	5 (7%)	24 (11%)
Location	Upper 1/3	1 (1%)	1 (1%)	2 (1%)
	Middle 1/3	41 (33%)	37 (49%)	78 (38%)
	Lower 1/3	31 (25%)	24 (31%)	55 (28%)
	Diffuse	39 (31%)	8 (10%)	47 (23%)
	Unknown	14 (10%)	7 (9%)	21 (10%)
Operation	Yes	8 (6%)	69 (90%)	77 (38%)
	No	118 (94%)	8 (10%)	126 (62%)
Aim of Surgery	Curative gastrectomy	0 (0%)	59 (77%)	59 (29%)
	Palliative gastrectomy	6 (5%)	6 (8%)	12 (6%)
	Bypass	2 (2%)	4 (5%)	6 (3%)

ECOG, Eastern Cooperative Oncology Group; WD, Well differentiated; MD, Moderate differentiated; PD, Poorly differentiated; SRC, Signet ring cell; EGC, Early gastric cancer

2. Patterns of skeletal metastasis

Of the 203 patients, 180 had skeletal metastasis involving multiple sites **(Table 2**). The most common site was the spine (86%), followed by the pelvis (53%) and rib (50%) **(Table 3)**. Skeletal metastasis to long bones developed in 93 patients. Upper extremities were involved in 67 patients, and lower extremities, in 65 patients. In 39 patients, the tumor metastasized to both extremities.

Thirty-one patients (15%) had skeletal metastasis alone without metastasis to other organs, and the remaining 172 patients had combined metastasis to other organs. The most common site of combined metastasis included distant lymph node (131 patients, 65%), followed by the peritoneum (80 patients, 39%) and liver (56 patients, 28%) **(Table 4)**. The numbers of patients with one, two, three, and four organs involved were 61 (30%), 63 (31%), 35 (17%) and 13 (6%), respectively.

Table 2. Bone metastasis patterns

	Solitary (%)	Multiple (%)	Total (%)
Bone only	5 (2)	26 (13)	31 (15)
Combined organ	18 (9)	154 (76)	172 (85)
Total	23 (11)	180 (89)	203 (100)

Table 3. Frequency of metastatic bone lesion

Metastatic bone site	Number (%)
Spine	175 (86)
Pelvis	108 (53)
Ribs	101 (50)
Extremities	93 (46)
Skull	49 (24)

Table 4. Frequency of combined metastasis

Metastatic organ	Number (%)
Lymph node	131 (65)
Peritoneum	80 (39)
Liver	56 (28)
Lung	44 (22)
Ovary	16 (8)

At the time of diagnosis, the median serum CEA was 7.8 ng/ml (range 0.3-20,000 ng/ml); CA 19-9, to 40 U/mL (range 0.1-20,000 U/ml); ALP, to 158 IU/L (range 36-5,334 IU/L); and LDH, to 523 IU/L (range 81-4,593 IU/L) **(Table 5)**.

Table 5. Baseline tumor markers according to the type of skeletal metastasis

	Synchronous group (n = 126)	Metachronous group (n = 77)	Total (n = 203)
CEA, ng/mL	10.3	5.4	7.8
median, [range]	[0.3-2,690.0]	[0.4-20,000]	[0.3-20,000]
CA19-9,U/mL	53.8	31.9	40.0
median, [range]	[0.1-20,000]	[0.1-20,000]	[0.1-20,000]
ALP, IU/L	177.5	153.0	158.0
median, [range]	[36.0-3,042.0]	[62.0-5,334.0]	[36.0-5,334.0]
LDH, IU/L	600.0	413.5	523.0
median, [range]	[136.0-4,593.0]	[81-1,898]	[81.0-4,593.0]

CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; ALP, serum alkaline phosphatase; LDH, lactate dehydrogenase

Changes in CEA, CA 19-9, ALP, and LDH values between the time of gastric cancer diagnosis and detection of bone metastasis were statistically significant in metachronous patients. Patients with bone metastasis have elevated levels of CEA, CA19-9, ALP and LD **(Table 6)**. Median values for tumor markers did not differ significantly between synchronous and metachronous patients.

Table 6. Changes in tumor markers between the time of gastric cancer diagnosis and detection of bone metastasis in patients with metachronous metastasis

	Baseline Median [range]	Bone metastasis Median [range]	p-value
CEA, ng/mL	1.3 [<0.01-133.30]	5.4 [0.37-20,000]	< 0.001
CA19-9, U/mL	13.3 [<0.01-2,880]	31.9 [0.10-20,000]	0.022
ALP, IU/L	70 [33-292]	153 [62-5,334]	< 0.001
LD, IU/L	293.5 [83-380]	413.5 [81-1,898]	0.003

CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; ALP, serum alkaline phosphatase; LDH, lactate dehydrogenase

Then, we evaluated the changes of the tumor markers between bone only metastasis and combined metastasis. As in **Table 7**, there were no statistical differences between bone only and combined metastasis in terms of tumor markers.

Table 7. Changes in tumor markers between bone only and combined metastasis

	Synchronous		Metachronous		Total	
	Bone only (n=11) Median [range]	**Combined (n=115) Median [range]**	**Bone only (n=20) Median [range]**	**Combined (n=57) Median [range]**	**Bone only (n=31) Median [range]**	**Combined (n=172) Median [range]**
CEA	10.2	12.2	7.9	4.8	8.8	7.73
	[0.6-212.7]	**[0.3-2,690]**	**[1.1-170.5]**	**[0.4-20,000]**	**[0.6-212.7]**	**[0.3-20,000]**
p-value	0.856		0.784		0.502	
CA19-9	4.6	79.2	17	61.0	15.8	76.5
	[0.1-756.0]	**[0.1-20,000]**	**[0.1-20,000]**	**[0.1-10,400]**	**[0.1-20,000]**	**[0.1-20,000]**
p-value	0.044		0.334		0.041	
ALP	140	181	236	147	172	154
	[36-2,157]	**[42-3,042]**	**[67-2,706]**	**[62-5,334]**	**[36-2,706]**	**[42-5,334]**
p-value	0.812		0.225		0.460	
LDH	242	647	633	413.5	372	524
	[240-584]	**[136-4,593]**	**[324-1,898]**	**[81-1,739]**	**[240-1,898]**	**[81-4,593]**
p-value	0.095		0.302		0.604	

CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; ALP, serum alkaline phosphatase; LDH, lactate dehydrogenase

3. Skeletal related events

The most common symptom of skeletal metastasis at diagnosis was local bone pain, which 98 (48%) patients reported. We defined a skeletal related events **(**SRE) as a symptomatic development that required emergency surgery or radiotherapy such as (impending) fracture, spinal cord compression, and hypercalcemia of malignancy. Overall, only six patients (3%) developed SRE at diagnosis or during treatment **(Table 8)**. Three patients suffered pathologic fractures, one developed paralysis, and two developed hypercalcemia.

Table 8. Skeletal related events in patients with synchronous and metachronous metastasis

		Synchronous (n= 126)	Metachronous (n= 77)	Total (n= 203)
SRE	Yes	1 (1%)	5 (6%)	6 (3%)
	No	125 (99%)	72 (94%)	197 (97%)
Fracture		0 (0%)	3 (4%)	3 (2%)
Paralysis		0 (0%)	1 (1%)	1 (1%)
Hypercalcemia		1 (1%)	1 (1%)	2 (1%)

SRE, Skeletal related events

4. Treatment outcomes

Median survival time after skeletal metastasis was 103 days (95% CI, 80-126 days). For patients with synchronous metastasis, median OS was 97 days (95% CI, 67-127 days) and for the metachronous group, 114 days (95% CI, 83-145 days); it did not differ significantly between these two groups. The median OS for patients with metastasis to bone only was 165 days (95% CI, 116-214 days), and for those with metastasis to bone and other sites, 97 days (95% CI, 74-120 days). However, this difference was not statistically significant (p=0.160).

As for the treatment, 120 (59%) patients received chemotherapy with or without local therapy. Remaining 83 patients received local therapy or supportive care only; 31 patients had radiotherapy and one patient had c-spine surgery followed by radiotherapy, and 52 patients received supportive care only. For chemotherapy regimen, 61 (51%) patients received taxanes, twenty-seven

(23%) patients received anthracycline, sixty-three (53%) patients with platinum (cisplatin, carboplatin, oxaliplatin), and 21 patients (18%) with irinotecan.

When we analyze survival according to the treatment modality, the median OS was 167 days (95% CI, 140-194 days) for the systemic treatment group and only 43 days (95% CI, 30-56 days) for the local treatment or best support group ($p<0.001$). The survival between two groups of radiotherapy only (n=31; 59 days, range 37-81) and supportive care (n=52; 39 days, range 23-55) did not differ ($p=0.272$). The supportive treatment group included patients with poor performance status and those who refused active treatment.

5. Prognostic factor analysis

In univariate analyses, poor performance status (ECOG 2-4) ($p<0.001$), multiple bone metastasis ($p=0.004$), high CEA (>7.8 ng/mL) ($p=0.006$), and high ALP (>158 IU/L) ($p<0.001$) showed significant adverse effects on survival **(Table 9)**. Parameters that were included in the multivariate analysis were age, performance status, existence of bone only metastasis, multiplicity of bone metastasis, non-skeletal (peritoneal, liver, and lung) metastasis, CEA, CA19-9 and ALP.

Table 9. Univariate analysis of prognostic factors for survival

Factors		MST (days)	95% CI	p-value
Age	≤51	114	94-134	0.132
	>51	93	55-131	
Gender	Male	93	64-122	0.706
	Female	118	87-149	
Performance status (ECOG)	0-1	122	102-142	<0.001
	2-4	38	21-55	
Histology	Intestinal type	110	68-152	0.333
	Diffuse type	100	74-126	
Metastasis Pattern	Bone only	165	123-207	0.120
	Combined	97	73-121	
Bone involvement	Solitary	184	112-256	0.004
	Multiple	95	73-117	
Peritoneal seeding	Yes	84	52-116	0.054
	No	120	88-152	
Liver metastasis	Yes	66	33-99	0.163
	No	118	97-139	
LN metastasis	Yes	100	74-126	0.572
	No	122	85-159	
Lung metastasis	Yes	70	54-86	0.120
	No	114	97-131	
Ovary metastasis	Yes	118	102-134	0.809
	No	101	74-128	
CEA (ng/mL)	≤7.8	123	92-154	0.006
	>7.8	99	76-122	
CA19-9 (U/mL)	≤40	129	91-167	0.137
	>40	93	60-126	

continued

Factors		MST (days)	95% CI	p-value
ALP (IU/L)	≤158	142	101-183	<0.001
	>158	66	47-85	
Treatment Modality	Systemic therapy CTx +/- RTx	167	140-194	<0.001
	Local treatment /Supportive care	43	30-56	

MST, median survival time; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LN, lymph node; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; ALP, serum alkaline phosphatase; LDH, lactate dehydrogenase; CTx, chemotherapy; RTx, radiotherapy

Using a stepwise Cox regression model, elevated ALP [Relative risk (RR) =2.00, P<0.001] and poor performance status [RR=2.11, p=0.003] independently predicted poor prognosis **(Table 10)**.

Table 10. Multivariate Cox regression analysis

	p-value	RR	95% CI
ALP >158 (IU/L)	<0.001	2.00	1.37-2.92
ECOG 3-4	0.003	2.11	1.28-3.46

RR, relative risk; CI, confidence interval; ALP, serum alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group

From our findings, we intended to identify a subgroup of patients who would potentially benefit from more aggressive treatment including systemic

chemotherapy. Based on multivariate analysis, we divided the study group into three subgroups, with 86 patients of none of adverse factors, 79 patients of only one adverse factor, and 30 patients of two adverse factors identified. The median survival times were 152 days (95% CI, 109-195 days), 82 days (95% CI, 50-114 days) and 29 days (95% CI, 12-46 days), respectively (P<0.0001) **(Figure 1)**.

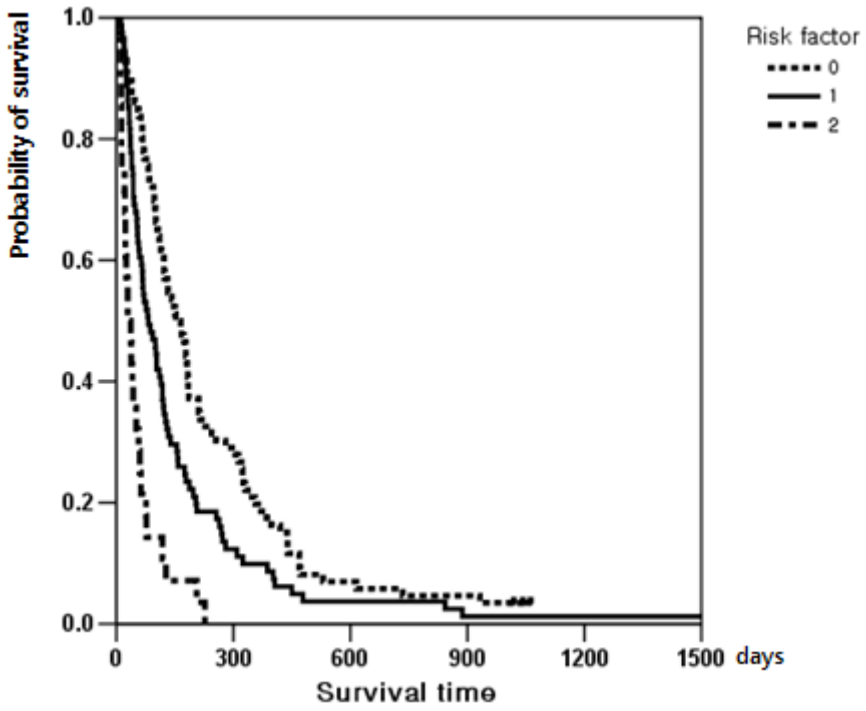

Figure 1. Subgroup analysis according to adverse factors in patients with skeletal metastasis

Among 165 patients who had none or one of the adverse factors, 108 patients (82%) were given palliative chemotherapy. As shown **Figure 2**, these patients survived longer than patients with radiotherapy or supportive care only (178 versus 52 days; p<0.0001). Among patients who had two adverse factors, survival times did not differ between those receiving palliative chemotherapy (n = 7; 57 days, range 42-72) and those receiving radiotherapy or best support (n = 21; 25 days, range 19-31) (p= 0.085) **(Figure 3)**.

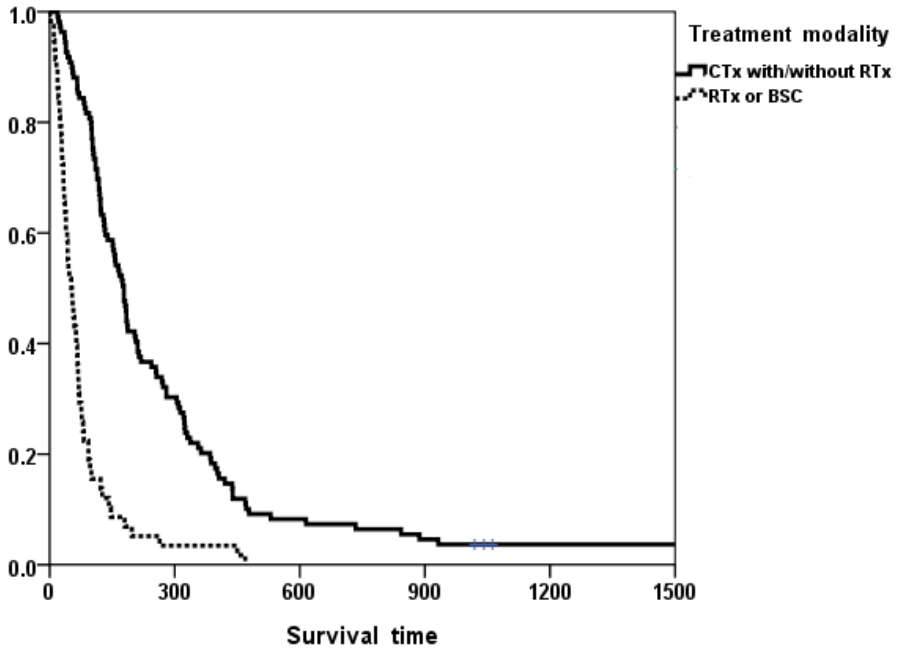

Figure 2. Subgroup analysis according to treatment modality in patients with none or only one of the identified adverse factors

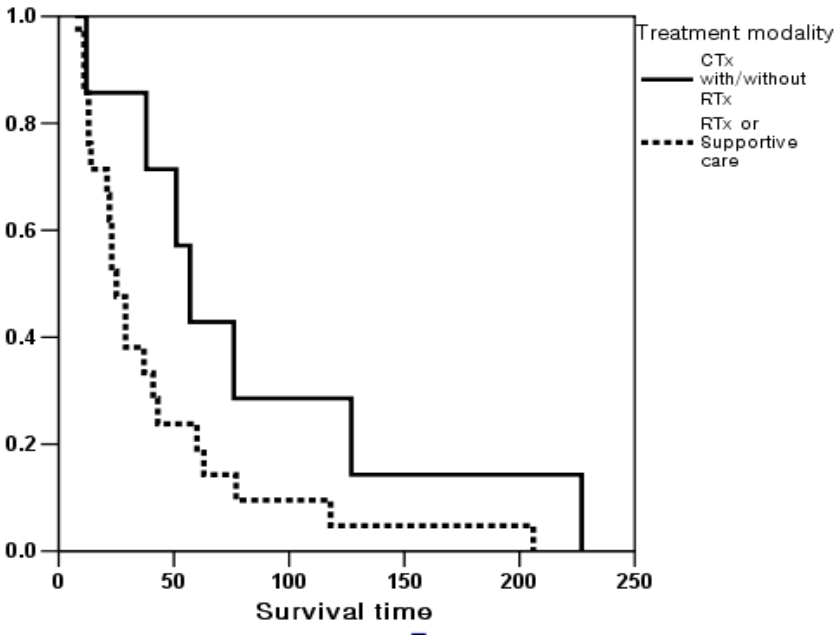

Figure 3. Subgroup analysis according to treatment modality in patients with two adverse factors

IV. DISCUSSION

The clinical features and optimal treatment for gastric cancer with bone metastasis have not been systematically investigated because this subset is relatively rare. Importantly, knowledge of prognostic factors to guide treatment of this group are still lacking. In this study, we aimed to investigate the clinicopathologic features, treatment outcomes, and factors that predict survival of patients with gastric cancer-related skeletal metastasis.

Although gastric cancer is thought to spread less often to the bone than to peritoneum or liver, the incidence of skeletal lesions is various from 1% to 45%. Mori *et al*. investigated 719 malignant tumors by autopsy,[9] including 176 gastric tumors. Twenty-eight of gastric tumors (16%) metastasized to bone, being the third most common site following liver and lungs. By contrast, Yoshikawa *et al*. and Yamamura *et al*. found a relatively low rate (1.2-1.4%) of skeletal metastasis following curative resection of gastric cancer [10, 11]. Our study show similar data that bone metastasis incidence of gastric resection and inoperable patients was 0.9% and 11.2%, respectively. By contrast, Choi *et al*. evaluated 234 patients of advanced gastric cancer, and reported 106 patients (45%) as metastatic bone lesions. But they evaluated skeletal metastasis only with bone scan and it is possible that bone scan could gives false positive results. The increased uptake seen on a bone scan is associated with osteoblastic activity and may be causes other than metastasis. This wide-range discordance

on the incidence of skeletal metastasis in the literature may reflect the histories of the patient cohorts, the time of evaluation, and the methods for determining bone pathology. There have been lots of studies based on autopsy. However, autopsy findings provide only the end-stage of failure which could be overestimated in view of clinical setting. By contrast, Gunderson and Sosin reported a re-analysis of the second-look laparotomy after resection of the primary tumor[13]. This approach is useful because it can reveal mechanisms of early recurrence. However, routine second-look surgery has not proven to be worthwhile in gastric cancer because of the poverty of data that assert earlier diagnosis does improve the patients' outcome. These findings confound data on the prevalence of skeletal metastasis, and since bone scintigraphy is not usually performed, asymptomatic bone metastasis may be underestimated. It is also possible that peritoneal or liver metastasis masks the clinical manifestation of bone metastasis.

The most common sites of bone metastasis were the spine, pelvis, rib, extremities and skull, data consistent with previous reports.[12,14] Hematogenous spread of gastric cancer may potentially occur through (1) the portal vein, (2) the venous system other than the portal vein, and (3) lymphatic channels into the systemic circulation. The high rate of spinal metastasis from gastric cancer may be related to the involvement of the paravertebral venous plexus[12,15]. Nakanishi *et al.*[16] analyzed the pattern of axial metastasis in bone only metastasis and found that gastric cancer also tends to involve thoracolumbar

vertebrae nearest the stomach. In our study, 24 (77%) of 31 patients with bone only metastasis had spinal involvement. These findings point to Batson's vertebral plexus as a probable route in skeletal metastasis. In addition, most patients in our study did not show liver metastasis, most venous drainage from the stomach proceeds by the portal vein, and bone metastasis is frequently associated with lymph node metastasis. These findings indicate a systemic route for tumor spread from lymphatic channels [11, 17, 18]. We think that this mechanism differs from that of liver metastasis, which typically proceeds by a hematogenous route through the portal vein.

It is not common to encounter gastric cancer patients with bone marrow dissemination in the clinic, bone marrow biopsy is not a routine clinical practice. Our patients underwent bone marrow biopsy in case of unexplained leucopenia/thrombocytopenia, disseminated intravascular coagulopathy and extensive bone metastasis especially pelvic bone. Ten patients (4.9%) were included in our study with combined bone marrow metastasis, and these patients had poorer survival (51 versus 110 days, $p<0.001$).

We thought that laboratory data may be implicated in the diagnosis and prediction of skeletal metastasis. We analyzed the changes in CEA, CA19-9, ALP, and LDH. Our results were similar to those of Choi at al.[12] and Seto at al.[14], who found a significant increase in ALP in skeletal metastasis. However, lack of control arm (group of skeletal metastasis-negative group) limit us to draw a more confirmatory conclusion about the role of ALP for early detection

of skeletal metastasis. Our study also found that other markers of CEA, CA 19-9 and LDH also elevated. Similar increases in CEA, CA 19-9 and LDH may occur, however, in other clinical conditions such as benign pulmonary disease, thyroid dysfunction and inflammatory conditions of the gastro-intestinal tract[19]. We thus believe that more specific biomarkers are needed to predict skeletal metastasis.

A metastatic bony site is of particular importance because sudden paralysis is not a rare event in patients with skeletal metastasis from gastric cancer. Manifestations of bone metastasis include pain, pathologic fractures and hypercalcemia. In other cancers, including those of the breast and prostate, bisphosphonates may reduce the risk and delay the onset of SRE[20, 21], and are routinely used for this purpose. Clinical features and treatment of other cancers with skeletal metastasis are well-established, but corresponding information for gastric cancer is limited. In the present study, the most common SRE was bone fracture (3 patients, 2%) followed by hypercalcemia (2 patients, 1%).

For 77 metachronous patients, the median time to skeletal metastasis was 16 months (range, 4 to 87). Yoshikawa *et al*. reported that skeletal metastasis occurred within 2 years of gastric surgery in 20 of 23 patients (87%)[10]. Nakanishi et al. reported a mean interval of 14 months (range, 3-65 months) between surgery and diagnosis of the skeletal metastasis [16].

The prognosis for patients presenting with bone metastasis is poor. Median survival for patients with advanced gastric cancer is to be less than 12 months[22]

Nakanishi *et al.* reported a mean interval of 60 days between the diagnosis of skeletal metastasis and death[16]. Despite this poor prognosis, we thought that palliative chemotherapy may extend survival of these patients[8, 23]. Our data support the survival benefit of systemic chemotherapy with an extension of survival to 167 days. Both palliative radiotherapy and chemotherapy are quite feasible for these patients, hence variables that predict treatment outcome should facilitate the selection of patients most likely to benefit.

In general, patients with solitary or few metastasis have a better outlook than those with multiple metastasis[22]. Our study supports this premise, and by multivariate analysis, identified several adverse factors that significantly influence survival. Patients with none or one of these factors showed a benefit from chemotherapy but those with two adverse factors did not. We would therefore advise these patients to consider chemotherapy depending on the presence of these factors.

One of the limitations of this study is to focus on survival only, not on quality of life. We cannot prove the effect of radiotherapy for alleviating symptom such as bone pain and paralysis in gastric cancer. Further studies are needed about quality of life for skeletal metastasis patients who receive radiotherapy or chemotherapy. However, the current findings indicate that skeletal metastases from gastric cancer have several distinctive manifestations. Although it is a difficult to decide both for physicians and patients whether to proceed with aggressive treatment, we recommend to administer more tailored

therapies stratified based on risk factors to enhance treatment outcome. Further analysis on larger series of patients for validation of the current results is warranted.

V. CONCLUSION

This study describes how knowledge of metastatic behavior may inform the diagnosis, treatment, and follow-up for patients with gastric cancer and skeletal metastasis. We recommend that treatment for gastric cancer with skeletal metastasis be tailored to the adverse factors of the individual patient, so as to extend survival and improve the quality of life. We believe that a better understanding of metastatic behaviors is helpful for diagnosis, treatment strategy, and method of followup for patients with skeletal metastases from gastric cancer.

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ABSTRACT

뼈전이를 동반한 위암환자의 임상양상 및 예후

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서론: 위암환자에 있어서 뼈 전이는 생존에 나쁜 영향을 미치는 예후 인자 중 하나이며, 질병의 경과 및 삶의 질을 악화시키는 인자로 알려져 있다. 하지만 지금까지 위암환자에서 발생한 뼈 전이에 관해서는 연구된 바가 거의 없다. 따라서 본 연구에서는 뼈 전이를 동반한 위암환자의 임상-병리적 특성, 치료 결과 및 예후 인자에 대해서 연구 하였다.

방법: 본 연구는 1998년 1월부터 2008년 5월까지 세브란스 병원에 내원하여 치료 받은 8633명의 환자들을 대상으로 의무기록을 후향적으로 검토하였다. 뼈 전이의 진단은 plain X-ray, Computed tomography(CT), Magnetic resonance imaging(MRI), ^{99m}Tc-labeled bone scan, ^{18}F FDG-PET scan을 시행하여 진단 하였다.

결과: 203(2.4%)명의 환자들에서 뼈 전이가 진단 되었고, 대부분 환자들의 분화도는 미분화형(poorly differentiated carcinoma) (n=147,

72%) 이었다. 126 (62%)명의 환자가 위암 진단 당시 뼈 전이를 진단 받았으며, 나머지 77명의 환자들에서 위암 진단 후 뼈 전이까지 걸린 시간은 중앙값 16개월(range, 4 to 87개월)이었다. 대부분의 환자들(180명, 86%)은 다발성으로 발생한 뼈 전이가 관찰 되었으며, 그 중 척추가 가장 흔한 전이 장소였다. 6(3%)명의 환자들에서 skeletal related events (SRE)가 발생 하였고, 이 중 3명은 병적 골절, 1명은 마비, 나머지 2명은 고 칼슘혈증을 경험 하였다. 치료는 120명의 환자에서 항암치료(±방사선치료)가 시행 되었으며, 나머지 83명의 환자에게는 방사선 치료 단독 또는 보존적 치료가 시행 되었다. 전체 환자의 중앙 생존값은 103일(95% CI, 80-126)이었다. 예후인자에 대한 다변량 분석을 하였을 때, ALP 상승[상대위험도 (RR) 2.00, $p<0.001$] 및 나쁜 전신상태[상대위험도 (RR) 2.11, $p=0.003$]가 나쁜 예후인자에 해당되었다. 1개 이하의 나쁜 예후 인자를 가진 환자에서 항암치료(±방사선치료)를 시행 하였을 때 방사선 치료 단독 또는 보존적 치료 군에 비해 생존률의 유의한 향상을 보였다.

결론: 본 연구는 뼈 전이를 동반한 위암환자의 예후인자를

예측한 첫 번째 연구이다. 앞으로 생존률 및 삶의 질을 개선하기 위해 각각의 환자들의 위험인자에 따른 맞춤치료가 필요하며 이에 대한 추가적인 연구가 더 진행 되어야 할 것이다.

핵심되는 말 : 위암, 뼈전이, 예후인자