

*Original research-Orijinal araştırma*

## Metastasis to bone from gastric cancer: a single centre experience

Mide Kanserinde Kemik Metastazı: Tek Merkez Deneyimi

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### Abstract

**Aim.** Bone metastasis is relatively uncommon with gastric carcinoma. Its complications have a negative impact on the quality of life and function of cancer patients. We planned a retrospective study to investigate the incidence and clinicopathological features of bone metastasis from gastric cancer and to explore the therapeutic outcome. **Method.** We retrospectively reviewed the clinical records of consecutive 253 patients with gastric cancer who admitted Outpatient Clinic of Medical Oncology in Hacettepe University. **Result.** Of 253 patients with gastric cancer, 26 patients (10.2%) were found to have skeletal metastases. The median age was 56 years. The vertebrae were the most frequent metastatic site (85%). Bone metastasis-related events (BMEs) included fracture, cord compression, severe bone pain, and radiation therapy because of the risk of fracture were found in 15 (58%) patients. Surgical treatment was given to 3 patients because of bone fracture and cord compression. The median survival was 130 days and 1-year survival was 27%. The median duration between diagnosis of skeletal metastasis and death was 68 days. Elevated alkaline phosphatase (ALP) level was associated with short survival. **Conclusion.** Skeletal metastasis-associated complications may significantly reduce the quality of life. Bone metastasis is a major health problem because of its complications including pain, pathologic bone fractures, and spinal cord compression.

**Key words:** Gastric cancer; bone metastasis; incidence; survival; complication.

### Özet

**Amaç.** Mide kanserinde kemik metastazı sık değildir. Kemik metastazı komplikasyonları kanser hastalarında fonksiyon ve yaşam kalitesi üzerine olumsuz etkiler yapmaktadır. Çalışmada mide kanseri olgularında kemik metastazı insidansı, klinikopatolojik özellikleri ve tedavi sonuçlarını değerlendirmeyi amaçladık. **Yöntem.** Hacettepe Üniversitesi Medikal Onkoloji polikliniğine başvuran 253 hastanın klinik kayıtları retrospektif olarak gözden geçirildi. **Bulgular.** Mide kanserli 253 hastanın 26'sında (%10.2) kemik metastazı bulundu. Ortanca yaş 56 idi. Vertebralar en sık metastaz yeri idi (%85). Fraktür, kord basısı, ciddi kemik ağrısı ve fraktür riski nedeniyle radyoterapi uygulaması gibi kemik metastazı ilişkili olaylar 15 (%58) olguda izlendi. 3 hastaya kord basısı ve kemik fraktürü nedeniyle cerrahi yapıldı. Ortanca sağkalım 130 gün ve 1 yıllık sağkalım %27 idi. Kemik metastazından ölüme kadar geçen ortalama süre 68 gün idi. Yüksek alkalin fosfataz (ALP) düzeyi kısa sağkalımla ilişkili idi. **Sonuç.** İskelet metastazına bağlı komplikasyonlar yaşam kalitesini anlamlı derecede azaltabilir. Kemik

metastazları, ağrı, patolojik kemik kırıkları ve spinal kord bası komplikasyonları nedeniyle önemli bir sağlık sorunudur.

**Anahtar kelimeler:** Mide kanseri; kemik metastazı; insidans; sağkalım; komplikasyon.

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### **Introduction**

Skeletal metastasis develops during the course of advanced cancer. Although bone is a common site of metastasis for the lung, breast, prostate, kidney, and thyroid carcinoma, metastasis to bone is relatively uncommon with gastric carcinoma. The incidence of bone metastases ranges between 0% and 17% in patients with gastric cancer [1, 2].

Skeletal metastases are often associated with significant morbidity. Common complications of bone metastasis include bone pain, symptomatic pathologic fracture, spinal cord compression, and hypercalcemia of malignancy. The other complications include pathologic fractures and hematologic disorders due to bone marrow involvement. Sudden paralysis may occur because of the fractures of vertebral metastasis. These complications have a negative impact on the quality of life, performance status, and function of cancer patients. The earlier diagnosis and making therapeutic decision are very important because of the serious morbidity of bone metastasis from gastric cancer.

Gastric cancer is the second frequent cancer in Turkey and the age-standardized ratio is approximately 10% [3]. There is limited information about the incidence and clinical course of bone metastasis from gastric cancer. We planned a retrospective study to investigate the incidence and clinicopathological features of bone metastasis from gastric cancer and to explore the therapeutic outcome.

### **Patients and Methods**

#### ***Study Population***

We retrospectively reviewed the clinical records of consecutive 253 patients with gastric cancer who admitted Outpatient Clinic of Medical Oncology in Hacettepe University Institute of Oncology between January 2001 and July 2006. All cases were assessable with a complete history physical examination, and blood tests included serum biochemistry, complete blood counts, carcinoembryonic antigen (CEA) and CA-19-9; gastroscopy; operative, pathological, and radiation therapy reports; and abdominal and chest computed tomographies (CT). Tumor staging was done according to Tumor-Node-Metastasis system. The presence of skeletal metastases (on bone scintigraphy, magnetic resonance imaging (MRI), and plain X-ray films), outcome parameters such as skeletal-related events including pathological fracture, radiation therapy, analgesic use, and survival were investigated.

#### ***Statistical Analysis***

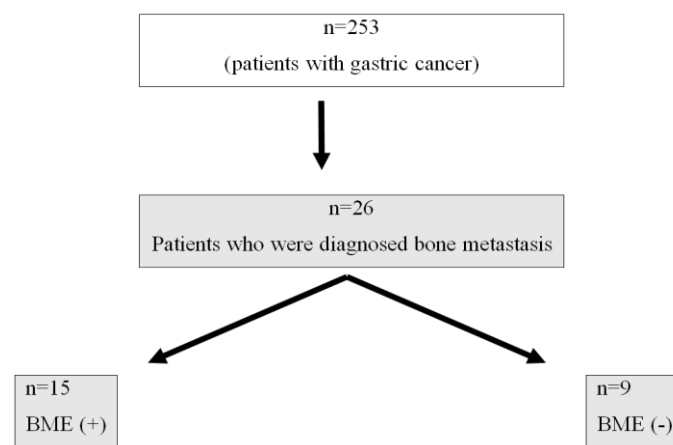
All statistical analyses were conducted using the statistical program SPSS 15.0 for Windows (SPSS, Chicago, IL, USA). A p value < 0.05 was considered statistically significant. The association of factors was evaluated by using the chi-square and Mann-

Whitney U tests. The duration of survival was defined as the interval between the dates of initial diagnosis of skeletal metastasis and death. Survival curves were obtained according to the Kaplan-Meier method.

## Results

### Patients

In the study, we evaluated 253 patients with gastric cancer (Figure 1). A total of 26 patients (10.2%) were found to have skeletal metastases during their clinical course. The patients' characteristics were displayed Table 1. Among them, 15 patients (58%) were men and 11 patients (42%) were female. The median age was 56 years (range: 19-79 years). The median age of female was lower than male (52 vs 59 years). Most patients had a good performance status Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$  in 14 patients, or 54%). The poorly differentiated type was the most frequent (19/26; 73%). Twenty-one out of 26 patients (81%) were found lower hemoglobin levels. Serum alkaline phosphatase (ALP) was higher in 14 (54%) patients



**Figure 1: The schema of the study (BME: Bone metastasis-related event)**

and serum lactate dehydrogenase (LDH) levels were higher in 11 (42%) patients. Hypercalcemia was found only 4 patients. Serum CEA level elevated in 15 patients and CA 19-9 elevated in 17 patients. Serum albumin level was low in 17 patients.

**Table 1. Characteristics and selected clinical data of study population.**

	n	%
Gender		
M/F	15/11	58/42
Median Age (year)	56 (19-80)	
ECOG PS		
$\leq 2$	14	54
$> 3$	12	46
Tumor differentiation		
Poorly	19	73
Well/moderate	7	27
Hemoglobin $< 12$ g/dL	21	81
LDH $> 460$ U/L	11	42
ALP $> 129$ U/L	14	54
Calcium $> 10.2$ mg/dL	4	15
CEA $> 5.0$ ng/ml	15	58
CA 19-9 $> 38$ ng/ml	17	65
Serum albumin $< 3.2$ mg/dL	17	65
BME	15	58

PS, performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; BME, bone metastases-related event; ECOG: Eastern Cooperative Oncology Group

Therapeutic irradiation for the metastatic site was administered to 12 patients for palliation of pain or prevention of fracture. Fifteen patients were given zoledronic acid 4 mg/day for every 4 weeks. Because of severe pain, 18 (69%) of the patients with bone metastasis required opioid analgesics. There were no association between serum LDH, and ALP levels and BMEs.

**Table 2: The site of bone metastasis**

	n	%
Vertebrae	22	85
Rib	11	42
Pelvic	9	35
Femur	6	23
Humerus	3	12
Scapula	1	4

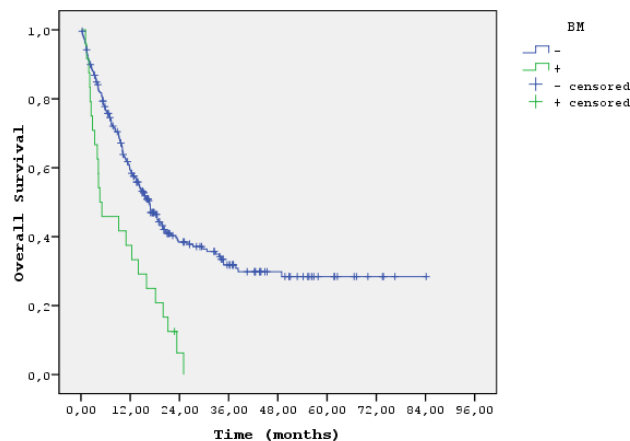
**Table 3: The treatment used in patients with BMEs**

	n	%
Surgery	3	12
Bone fracture	2	8
Cord compression	1	4
Radiotherapy	12	46
Hypercalcemia	4	15
Pain required opioid analgesics	18	69
Zoledronic acid	15	58

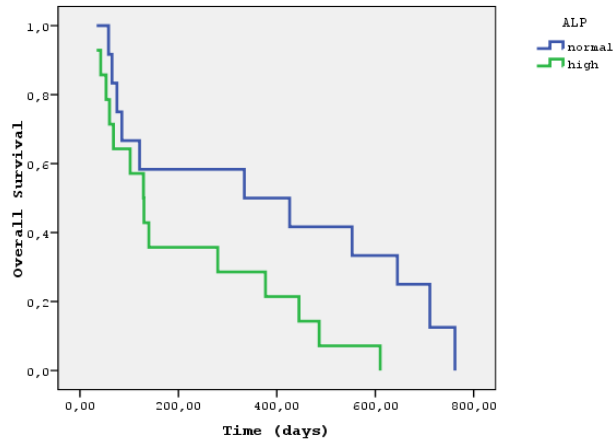
BMEs: Bone metastasis-related events

### Survival

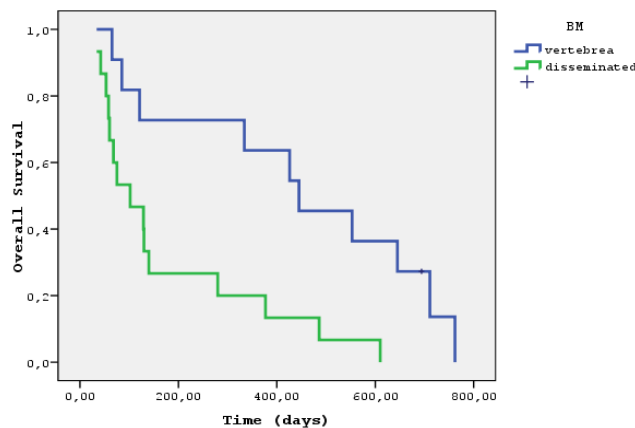
Although median survival was 507 days for all patients, for patients with skeletal metastasis were 130 days ( $p<0.0001$ ) (Figure 2). For the patients with bone metastasis, 1-year survival was 27%. The median duration between diagnosis of skeletal metastasis and death was 68 days. Higher serum ALP ( $p=0.050$ ) were significantly shorter than those without BMEs and normal serum ALP (Figure 3). In cases with isolated vertebrae metastasis, the median survival was significantly longer than disseminated bone metastasis (102 days vs. 445 days;  $p=0.005$ ) (Figure 4).



**Figure 2: The overall survival for bone metastasis from gastric cancer ( $p<0.0001$ )**



**Figure 3: The survival curve of alkaline phosphatase on the prognosis (p=0.050)**



**Figure 4: The survival curve of dissemination of bone metastasis (BM) (p=0.005)**

## Discussion

In patients who were diagnosed with gastric cancer, the most common site of metastasis is the adjacent lymph nodes, liver, lung, and peritoneum. Mechanism of bone metastasis in stomach cancer has still unclear. There are several possible mechanisms explained with metastasis to bone of gastric cancer. Firstly, gastric mucosa has a rich supply of blood capillaries which are adjacent to the basal lamina [4]. Lenhert et al. [5] proposed that the rich supply of blood capillaries in gastric mucosa may contribute to bone metastasis. Secondly, metastasis to spine may be through the paravertebral venous plexus as proposed by Batson [6]. According the theory, the flow into the vertebral veins is to tend to predominate because intrathoracic or intraabdominal pressure is increased. Lastly, gastric cancer might metastasize to the bone through the thoracic duct [7].

Many studies revealed that the bone metastasis was more frequent in poorly differentiated gastric cancer [8, 9]. Bone metastasis is associated with the poorly differentiation and the rate of bone metastasis ranges between 40% and 86% in these patients [1, 8-10]. In this study, 19 (73%) patients with metastasis to bones had poorly differentiated gastric cancer. The results of our study were similar to the literature.

The spine, the ribs, pelvis, femur, and skull are the most frequent metastatic sites [11]. The metastasis of the other sites including clavicle, sacroiliac joint, humerus, and sternum is uncommon. In the study, the ten percentages of patients who have diagnosed gastric cancer found bone metastasis. The spine (84.6%), especially thoracolumbar vertebrae, is the most frequent metastatic site, followed by the ribs and femur. Bone fractures (neck of

femur, thoracic vertebrae and rib) showed in 3 cases because of metastasis. The overall survival was markedly shorter in patients with bone metastasis compared to those without. The overall survival in patients with gastric cancer who were diagnosed bone metastasis was 130 days and 1-year survival found 27%. The median duration from bone metastasis to death was 68 days. In a study, authors reported that the interval from diagnosis of gastric cancer to vertebral metastasis was 6.9 months [12]. After vertebral metastasis, 1-year survival was 0% and 15.3% at 6-months and the survival rate from vertebral metastasis was 15.3% at 6 months and 0% at 1 year. Nakanishi et al [10] reported the results of their study, which included 48 patients with skeletal metastasis from gastric cancer. They found that the mean survival after diagnosis of skeletal metastasis was 60 days and the mean period between surgery and diagnosis of skeletal metastasis was 14 months.

Although there was no tumor markers used for the diagnosis of bone metastasis, many cases with bone metastasis were found to have elevated serum ALP. Choi et al [11] found that ALP elevated in 64% of patients with bone metastasis. Similarly, Seto et al [13] also reported that ALP was significantly elevated in patients with bone metastasis of gastric cancer. In our study, we found that the levels of serum ALP and LDH at the time of diagnosis of bone metastasis elevated in patients with bone metastasis compared to those without metastasis. Hypercalcemia was only seen in 4 cases, but elevated serum ALP and LDH were detected in 3 out of 4. In patient with gastric cancer, serum elevated levels of ALP, LDH, and calcium might indicate bone metastasis.

Although metastasis to bone from stomach is uncommon, it is very important because of its complications. Pain due to bone metastases is the most frequent form of pain reported by cancer patients [14]. It is the most discomfort symptom in patients with bone metastasis and is responsible for reduction of the quality of life. Non-steroidal anti-inflammatory drugs were used to treat bone metastasis-related pain. But, patients with severe pain require opioid analgesics. The other complications include pathological bone fracture, hypercalcemia, cord compression and sudden paralysis. Complications such as spinal cord compression and fracture of long bones and vertebrae often require surgery or radiotherapy. Both of the complications may markedly reduce the quality of life. Radiotherapy was also used to control the severe pain and to prevention the fracture. In a published study by Nakanishi, pain in 33% of patients with skeletal metastasis was palliated by radiation therapy [10]. Zoledronic acid, which is bisphosphonates, is useful to treat of metastasis-related hypercalcemia and to prevent of bone fracture [15]. In summary, the cost of treatment of bone metastasis may be higher in patients developed complications.

In conclusion, skeletal metastasis-associated complications may significantly reduce the quality of life. Bone metastasis is a major health problem because of its complications including pain, pathologic bone fractures, and spinal cord compression. Palliative therapy such as radiation therapy, surgery, biphosphanates, and conventional analgesics (NSAIDs) and opioid analgesics could be recommended for patients with skeletal metastasis from gastric cancer.

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