

Metastatic bone cancer as a recurrence of early gastric cancer - characteristics and possible mechanisms

Michiya Kobayashi, Takehiro Okabayashi, Takeshi Sano, Keijiro Araki

Michiya Kobayashi, Takehiro Okabayashi, Keijiro Araki, Department of Tumor Surgery, Kochi Medical School, Nankoku 783-8505, Japan
Takeshi Sano, Gastric Surgery Division, National Cancer Center Hospital, Chuo-ku, Tokyo 104-0045, Japan
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Correspondence to: Michiya Kobayashi MD, PhD, Department of Tumor Surgery, Kochi Medical School, Oko-cho, Nankoku, Kochi 783-8505, Japan. kobayasm@kochi-ms.ac.jp
Telephone: +81-888-80-2370 Fax: +81-888-80-2371
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Abstract

The surgical outcome of most early gastric cancer (EGC) is usually satisfactory. Some cases show bone metastasis even though the depth of cancer invasion is confined to the mucosa. The most frequent site for recurrence of EGC is the liver. Cases of EGC with bone metastasis are reviewed to clarify the clinicopathological characteristics of EGC giving rise to bone metastasis. Possible mechanisms and risk factors underlying this rare condition are proposed. Forty-six cases of bone metastasis from EGC are reviewed from published reports and meeting proceedings in Japan. This investigation suggests that risk factors for bone metastasis from EGC include depressed-type signet-ring cell carcinoma, poorly differentiated carcinoma, and/or the likely involvement of lymph node metastasis, even though the cancer is confined to the gastric mucosa. The risk factors do not include recurrence of EGC in the liver. We speculate that the mechanism of bone metastasis from EGC is via lymphatic channels and systemic circulation. Post-operative follow-up of cases should consider the development of bone metastasis from EGC. We propose the use of elevated alkaline phosphatase levels for the detection of bone metastasis and recommend bone scintigraphy in positive cases.

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Key words: Gastric cancer; Early gastric cancer; Bone metastasis; Recurrence of early gastric cancer

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INTRODUCTION

Early gastric cancer (EGC) is defined as a cancer confined

to the mucosa or submucosa regardless of lymph node metastasis and/or distant metastasis. Although the 5-year survival rate for EGC is 90% or greater^[1], EGC can recur. Most of the recurrences from EGC are hematogenous metastasis of the liver. Bone metastasis is a common event in advanced cancers of the breast, lung and prostate, but not in gastric cancer (GC). We have previously reported a rare case of mucosal EGC giving rise to multiple bone metastases^[2].

In this article, we reviewed bone metastasis from EGC through a literature search of published reports and meeting proceedings in Japan. We have discussed the possible mechanisms and risk factors underlying this rare condition.

RECURRENCE OF EGC

Ichiyoshi *et al.*, reviewed 503 consecutive cases of curative resection for EGC at a single institution from 1965 to 1988^[3]. Seventeen patients (3.4%) died from a recurrence of GC. Of these 17 cases, 9 with submucosal invasion developed hematogenous metastasis in the liver, lung or bone. These cases showed that high-risk factors for hematogenous recurrence included submucosal cancers with a macroscopically elevated lesion, lymph node metastasis, and vessel invasion^[4].

Sano *et al.*, investigated the follow-up records of 1 475 EGC cases treated at the National Cancer Center Hospital Tokyo^[4]. Twenty patients (1.4%) developed a recurrence of GC, including 14 (70%) with the lymph node metastases and 13 (65%) with blood-borne metastases. The incidence of recurrence of GC was shown to be significantly higher in submucosal, node-positive, and histologically differentiated carcinomas than in mucosal, node-negative, and undifferentiated groups. Hematogenous metastasis was thought to be the most common mode of recurrence and the investigation by Sano *et al.*, showed that hematogenous recurrence of EGC accounted for 68% of 91 histologically differentiated tumors and 34% of 32 undifferentiated tumors^[4]. This review also showed that lymph node metastasis at the time of surgery was not related to the mode of recurrence.

Lee *et al.*, investigated 1 452 EGC patients with curative resection at Seoul National University Hospital in Korea from 1986 to 1995^[5]. Twenty-one patients (1.4%) showing recurrence of GC included four cases with locoregional disease, two with peritoneal disease, nine with distant recurrence, and six with a mixed pattern of recurrence. Using multivariate analysis Lee *et al.*, concluded that EGC with lymph node metastasis carries a high risk of recurrence.

Guadagni *et al.*^[6], investigated 172 EGC patients who underwent gastrectomy at seven institutes in Italy. Twelve patients (7.0%) developed a recurrence of GC after surgery. Of these, three had liver metastasis, two had lymph node

recurrence, four had peritoneal disease and five had recurrence of GC in the gastric stump. The two cases with lymph node metastasis also had peritoneal dissemination. The most frequent site of recurrence was the gastric stump and Guadagni *et al.*, concluded that recurrence in this location may be related to inadequate histological examination of resection margins. They suggested that submucosal and intestinal type cancers were a high risk factor for recurrence of GC.

Kodama *et al.*, investigated 167 EGC cases and proposed growth patterns for EGC^[7]. They classified a carcinoma growing expansively with complete destruction of the muscularis mucosae as Pen A-type. The characteristics of Pen A-type carcinoma were elevated lesions (87.5%), histological differentiation (81.3%), a high incidence of lymphatic metastasis and frequent hematogenous metastasis. The most common site of recurrence for this type of cancer was liver metastasis within 3 years^[7].

According to the reports discussed above, the recurrence of EGC occurs in 1.4-3.4% of surgically resected cases. Macroscopically elevated, submucosal, lymph node positive, and histologically differentiated cancer types show a higher incidence of recurrence than their counterparts. The most common mode of recurrence is hematogenous metastasis of the liver. Bone metastasis is rare, even in cases with hematogenous recurrence of GC.

LYMPH NODE METASTASIS IN EGC

The most important prognostic factor for patients with EGC is the presence of lymph node metastasis. Lymph node metastasis of EGC is found in 5.4-24.0% of cases. Sano *et al.*, investigated the clinicopathological features of 748 solitary EGC cases and found that only depth of invasion (submucosal invasion) and tumor size (more than 2 cm) significantly correlated with lymph node metastasis^[8]. Maehara *et al.*, analyzed 396 EGC cases and found that lymphatic involvement, in addition to depth of invasion and tumor size, were independent risk factors for the occurrence of lymph node metastasis^[9]. Lehnert *et al.*, reported that the rate of lymph node metastasis of mucosal and submucosal EGC is 4.2% (of a total of 1 447 cases) and 16.8% (of a total of 1 509 cases), respectively^[10]. Gotoda *et al.*, reported that the rate of lymph node metastasis from intramucosal cancer was 2.2%^[11] and for differentiated and undifferentiated mucosal carcinoma was 0.4% and 4.2%, respectively. They showed that lymph node metastases from differentiated and undifferentiated submucosal cancer were 17.0% and 15.1%, respectively^[11].

Although metastases occurs most commonly in peri-gastric nodes, Kawata *et al.*, identified 16 EGC cases, until 1991 in Japan, with distant lymph node metastasis. Most of these cases showed submucosal invasion, only two had mucosal EGC, one case had bilateral inguinal lymph node metastasis, and one had paraaortic lymph node metastasis^[12].

BONE METASTASIS IN GC

Bone metastasis is a rare condition in GC and is clinically underestimated. Mori *et al.*, investigated 719 cases of malignant tumors among 2 240 consecutive autopsies^[13] in Tokyo

Medical and Dental University. These included 176 cases of GC of which 28 cases (15.9%) exhibited metastasis in bone, the third-most common site of GC metastases. The metastatic rate in the liver and lungs was 34.7% and 31.3%, respectively. Consistent with these findings, Yoshikawa and Kitaoka and Yamamura *et al.*, showed that the metastatic rate in bone from curatively resected GC cases was high among autopsy cases, but was comparatively low in clinical practice at a rate of 1.2-1.4%^[14,15]. Also in support of these findings, Maeyama *et al.*, reported the rate of bone metastasis in clinical practice and autopsy as 0.7% and 17.6%, respectively.

Choi *et al.*, evaluated bone metastasis from GC by bone scintigraphy^[16]. They investigated 234 bone scans from a total of 17 176 GC patients. The 234 patients were classified according to their original clinical stage rather than by standard stage and were identified as having advanced stage disease. Of these cases, 106 (45.3%) had metastatic bone lesions.

The findings discussed above suggest that asymptomatic bone metastasis is underestimated as examination by bone scintigraphy is not a routine clinical practice. It is also possible that peritoneal dissemination or liver metastasis masks the clinical manifestation of bone metastasis. For these reasons, the rate of bone metastasis in clinical cases may be higher than expected.

OTHER DETECTION METHODS FOR BONE METASTASIS FROM GC

Maehara *et al.*, investigated bone micrometastasis using a monoclonal anti-cytokeratin antibody^[17]. They found that 9 (20%) of 45 EGC cases examined had cytokeratin-positive cells in the bone marrow at the time of primary surgery. Microvessel density in the primary tumor was significantly higher in cytokeratin-positive than in cytokeratin-negative patients. These findings suggested that the presence of micrometastatic cells in the bone marrow was closely related to angiogenesis in the primary tumor.

Immunocytochemistry was performed by Macadam *et al.*, to investigate recurrence of GC^[18]. In this study, the monoclonal antibody Ber-EP4 that recognizes 34 and 39 ku glycopeptides present in human epithelium, was used to detect cells derived from squamous and columnar epithelial tumors. Of 74 patients with esophago-gastric cancer, 27 (36.5%) had Ber-EP4 positive cells in their bone marrow at the time of operation. Fourteen patients with benign gastrointestinal disease were used as a control group. There were no patients with clinical evidence of overt bone metastases, pathological fractures or signs of bone marrow fracture. Multivariate analysis of risk factors revealed that bone marrow cytology was a significant factor for recurrence and death.

While investigations on bone marrow micrometastasis by immunocytochemistry may play a role in predicting disease recurrence, at present it cannot be clinically applied to detect bone metastasis.

REVIEW OF EGC CASES GIVING RISE TO BONE METASTASIS IN THE JAPANESE LITERATURE

Cases of EGC giving rise to bone metastasis in Japan were

reviewed from literature and meeting proceedings in English or Japanese. Kodama *et al.*, reported 13 cases of GC recurrence out of 167 EGC cases, of which 5 had liver metastasis and 1 had bone metastasis^[7]. The case of bone metastasis was classified as 'small mucosal type', defined as a carcinoma lesser than 4.0 cm in diameter with mucosal invasion or slight submucosal invasion. This case was thought to be a premature type of carcinoma that had invaded the submucosa in a wide-penetrating fashion^[7]. Most 'small mucosal type' carcinomas are depressed lesions (73.8%) unlike the Pen A-type, which possess the potential for liver metastasis^[7].

In a previous report we, reviewed 46 bone metastasis cases arising from EGC in Japan to the end of 2003^[2]. These cases were used to clarify the clinicopathological characteristics of EGC leading to bone metastasis. It is possible that in some cases, metastatic bone cancer is not recognized as a recurrence of EGC. Table 1 summarizes the clinicopathological data from this study. Although more than half of the patients were females, the male to female ratio for EGC is 2:1. The incidence of mucosal and submucosal cancer was almost identical. Macroscopically, 34 out of 36 lesions were depressed or flat type. Histological characteristics were described for 48 lesions in the 44 cases. Twenty-three lesions were classified as signet-ring cell carcinoma, 14 as poorly differentiated adenocarcinoma and 2 as undifferentiated carcinoma. These characteristics differed from the histological type of EGC overall^[4,5]. The macroscopic features (poor histological differentiation and depressed shape) of lesions of EGC cases with bone metastasis were clearly different from those exhibiting liver metastasis^[3,4,19]. A description of lymph node status was available for 29 cases. The rate of lymph node metastasis was 55.2% (16 cases) and represented a higher rate of lymph node involvement compared with EGC as a whole^[8,9,11,20].

The time interval between diagnosis of EGC and bone metastasis was described for 40 cases out of 46 cases. Fourteen cases had bone metastasis at the time of diagnosis for EGC. In 26 cases, bone metastasis was diagnosed metachronously. The mean time interval to the development of metachronous bone metastasis after surgery was 46.9 mo, classified as a late recurrence of EGC. There were seven cases in which bone metastasis was diagnosed more than 5 years after surgery and two cases that presented with bone metastasis 96 mo after surgery (one from a meeting proceeding in Japan and the other a case report written in Japanese).

Concomitant metastasis, other than lymph node metastasis, was described in 16 out of the 46 cases and are summarized in Table 2. Lung metastasis was present in 11 cases (68.8%) and liver metastasis was observed only in 4 cases (25.0%). These findings are consistent with the finding by Seto *et al.*, that 60% of cases with bone metastasis cases arising from GC did not have liver metastasis^[21]. Similarly, a lack of liver metastasis is characteristic of cases of EGC with bone metastasis. It appears that liver metastasis has a different pathogenesis from bone metastasis arising from EGC.

POSSIBLE MECHANISMS RESPONSIBLE FOR BONE METASTASIS

Lehnert *et al.*, used light and transmission electron microscopy

Table 1 Clinicopathological features of early gastric cancer cases giving rise to bone metastasis in Japan

Age (range) (n = 37)		56.6 (33-78)
Sex (n = 43)	Male	18
	Female	25
Location (n = 28)	Upper third	4
	Middle third	13
	Lower third	7
	Whole stomach	4
Depth (n = 35)	Mucosa	18
	Submucosa	17
Timing (n = 40)	Synchronous	14
	Recurrence	26
Diagnosis (n = 24)	Plain bone X-ray	8
	Bone scintigraphy	13
	Autopsy	1
	Fracture	1
	Bone marrow aspiration	1
Macroscopic type ¹ (n = 36)	IIa	2
	IIb	6
	IIc	21
	IIc+III	5
	IIa+IIc	1
	IIb+IIc	1
Histological type ² (n = 48)	Tub	9
	Por	14
	Sig	23
	Ud	2
Lymph node metastasis ³ (n = 29)	n0	13
	n1	5
	n2	4
	n3	3
	n4	4

¹IIa: elevated type, IIb: flat type, IIc: depressed type, III: excavated type, ²tub: tubular adenocarcinoma, por: poorly differentiated adenocarcinoma, sig: signet-ring cell carcinoma, ud: undifferentiated carcinoma, and include cases with multiple lesions. ³The General Rules for the Gastric Cancer Study (The 12th Edition), Japanese Research Society for Gastric Cancer.

Table 2 Distant metastatic sites other than lymph node of early gastric cancer with bone metastasis (n = 16, nine cases that had more than two distant metastasis are included)

Lung	11
Liver	4
Brain	2
Kidney	2
Pleura	2
Ovary	2
Meninx	2
Spleen	2
Thyroid	1
Peritoneum	1
Diaphragm	1

to investigate lymph and blood capillaries of human gastric mucosa and found that the upper and middle levels of the lamina propria of the gastric mucosa contained no lymph capillaries^[10]. The mucosa has a rich supply of blood capillaries, many of which are adjacent to the basal lamina of gastric glands and surface epithelium^[6]. Lehnert *et al.*, suggests that the low incidence of lymph node metastases in the early mucosal GC might be explained by the rarity of lymph vessels in the mucosa, and that blood-borne metastases in

recurrent EGC might be related to the rich vascularity of the gastric mucosa^[10].

As there are no lymphatic vessels in the bone marrow, bone metastasis is usually regarded as a hematogenous spread^[22]. Rino *et al.*, reported five EGC cases without vascular invasion (n_0) resulting in bone metastasis^[23] and concluded that high risk factors for bone metastasis were accompanying ulceration, lymph node metastasis, and distant metastasis to other organs^[23].

Our review of the literature found that EGC resulting in bone metastasis had different macroscopic and histological types, suggesting that the mechanisms responsible for bone metastasis might not be through regular hematogenous routes via the portal vein as in liver metastasis. This is supported by the fact that concomitant metastasis was much more frequent in the lung than in the liver. We speculated that GC might metastasize to the bones through the vertebral vein system as suggested by Batson^[24]. Yamamura *et al.*, reported that GC with bone metastasis resulted in the invasion of the lymphatic vessels more frequently than invasion of venules^[15]. They also speculated that GC might metastasize to the bone through the thoracic duct.

For EGC, cancer cells may invade the capillary network or postcapillary venules in the gastric mucosa as mentioned in the investigation of Lehnert *et al.*^[10]. Alternatively, they may metastasize to regional lymph nodes following cancer cell invasion into the venules of lymph nodes as reported by Rino *et al.*^[23]. The latter is supported by the higher rate of lymph node metastasis in those cases with bone metastasis compared to that for EGC as a whole. For advanced cancer that has invaded adjacent organs, cancer cells may invade a fairly large vein, such as those found in the vertebral vein system outlined by Seto *et al.*^[21].

The possible mechanisms of hematogenous metastasis of GC are: (1) through the portal vein, (2) through the venous system, other than the portal vein, and (3) through lymphatic channels into the systemic circulation. Most cases of bone metastasis do not show liver metastasis, most venous drainage from the stomach is via the portal vein, and many cases of bone metastasis are associated with lymph node metastasis, suggesting that the mechanisms underlying bone metastasis involves lymphatic channel into the systemic circulation.

CLINICAL FEATURES AND TREATMENTS OF BONE METASTASIS

Ell reviewed skeletal imaging of metastatic diseases and identified MRI as sensitive in detecting bone marrow involvement^[25]. Despite this finding, bone scintigraphy continues to be the modality of choice in view of its simplicity, low cost, and ability to screen the entire body^[25]. Choi *et al.*, evaluated bone metastasis from GC by Tc-99m MDP imaging^[16]. They investigated 234 bone scans of GC patients. One hundred and six patients (45.3%) had bone scan abnormalities that qualified as metastatic bone lesions. The most frequent metastatic sites were the spine (66%), the ribs (59%), pelvis (43%), femur (30%), and skull (22%)^[16]. The least frequent metastatic sites were the shoulder girdle (17%), such as the scapula and clavicle, sacroiliac joint

(7.2%), humerus (6.0%), sternum (4.2%), and tibia (3.0%)^[16]. On the other hand, roentgenographic evaluation of bone metastases has limited value because symptoms caused by bone metastases frequently occur before abnormal imaging. Bone metastases were diagnosed by bone scintigraphy in 13 out of 24 cases described in our review.

Laboratory data may be helpful in the diagnosis of bone metastasis. Although tumor markers do not play an important role, many cases with bone metastasis show elevated serum alkaline phosphatase (ALP). In the study by Choi *et al.*, ALP was elevated in 64% of 106 patients with bone metastasis^[16]. Seto *et al.*, also found that ALP was significantly elevated in GC cases with bone metastasis compared to those without^[21].

Once cancer disseminates to the bone marrow, disseminated intravascular coagulation (DIC) may occur. Clinically, patients show a tendency to bleed that is confirmed on a combination of laboratory data for platelet count and fibrin degradation products. Several chemotherapy regimens for bone metastasis of GC have been reported as case reports. Kobayashi *et al.*, and Hironaka *et al.*, demonstrated that sequential methotrexate and 5-fluorouracil chemotherapy resulted in a high rate of alleviation (80% and 89%, respectively) of DIC caused by bone metastasis from GC^[26,27].

CONCLUSION

The incidence of bone metastasis from GC may be underestimated, and may occur after surgical resection in EGC. The mechanisms underlying bone metastasis arising from EGC most likely involve the lymphatic channels. Some cases give rise to late bone metastasis after surgery. As only 46 cases of bone metastasis arising from EGC are reported in Japan up to 2003, the exact incident rate cannot be estimated accurately. It can be considered that bone metastasis arising from EGC is a rare condition and as a result adjuvant chemotherapy is not recommended. In the post-operative follow-up of EGC cases that are histologically less differentiated and display involvement of lymph nodes, recurrences as bone metastasis should be considered. Elevation of ALP can be used to detect bone metastasis and bone scintigraphy is recommended for its diagnosis.

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