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ORIGINAL ARTICLE

Metachronous Liver Metastasis from Early Gastric Cancer

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Abstract
Introduction Early gastric cancer (EGC) has an excellent prognosis, but tumors recur in some patients even after apparently successful treatment. Among recurrent sites, the liver is one of the most common. In this study, we investigated clinicopathological features and factors predicting the development of liver metastasis from EGC.
Patients and Methods We examined the medical records of 2,707 consecutive patients who underwent open gastrectomy for EGC (pT1; m, sm) between 1991 and 2005. We assessed clinicopathological features and predictive factors for EGC metastasis in the liver.
Results Fifteen (0.6%) of the 2,707 patients developed liver metastasis. All primary gastric tumors of patients with liver recurrence demonstrated invasion to the submucosal layer. Macroscopically, nine patients had elevated-type and six depressed-type. Nodal metastasis was documented in seven patients (47%). Lymphatic and vascular involvements were seen in 11 (73%) and 7 (47%) patients, respectively. Multivariate analysis of patients with submucosal invasion revealed macroscopic elevated type and vascular involvement to be independent risk factors for liver metastasis.
Conclusions With submucosal cancer, the macroscopic elevated type and vascular involvement are significant predictive factors for EGC recurrence in the liver.

Keywords Early gastric cancer · Liver metastasis · Predictive factor

Abbreviations
ECG Early gastric cancer

Introduction

Although surgery is accepted as the optimal treatment for gastric cancer, distant metastases can be intractable and are often not surgically treatable. Early gastric cancer (EGC) has an excellent prognosis, with 5- and 10-year survival rates of more than 90% and 85–90%, respectively.[1–5] However, some patients experience cancer recurrence even after curative gastrectomy. Previously reported EGC recurrence rates range from 1.3% to 13.8%.[2,4–8]

Generally, the pattern of relapse after curative gastrectomy for EGC can be classified into hematogenous, lymphogenous and peritoneal metastasis, and other gastrointestinal cancers can also develop. Several investigators have reported hematogenous to be the most common form of relapse in patients with EGC[7,8] and that the most frequent metastatic site is the liver.[7–9]

We investigated EGC patients with relapse after curative gastrectomy, focusing particularly on liver metastasis. The aim of this study was to evaluate clinicopathological features and risk factors predicting liver recurrence from EGC.

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Patients and Methods

We examined the medical records of 2,707 consecutive patients who underwent open gastrectomy for EGC between 1991 and 2005 at the National Cancer Center Hospital, Tokyo. All cases were pathologically confirmed to have either mucosal or submucosal invasion. D2 lymphadenectomy were performed with curative intent. Adjuvant therapy was not allowed before the recurrence of cancer.

Information was obtained from follow-up records and the city registry office. The median follow-up period was 85.9 months. Postoperative follow-up included clinical and laboratory examinations every 6 months for the first 2 years, and annually thereafter until at least 6 years after operation. The follow-up enhanced computed tomography (CT) or ultrasonography was performed as a regular checkup. The last follow-up date was March 31, 2011. Only 52 patients (1.9%) were lost to follow-up within the 5-year period of this study.

Forty-eight patients (1.8%) developed cancer recurrence. Sites of initial relapse are shown in Table 1. Metastasis to the liver was seen in 15 patients (31%), followed by lymph nodes (27%) and bone (17%). Two of 48 patients had a few different metastatic sites as initial relapse. One with two different metastatic patterns had both bone and lung recurrences and the other patient with three metastatic patterns had bone, lung, and lymph node. But 15 liver metastasis cases have no other sites of recurrence initially.

Pathological results were categorized according to the Japanese classification of gastric carcinoma.[10] Macroscopically, the tumors were classified as elevated-type (l, IIa, IIa+IIc), flat-type (IIb), or depressed-type (IIc, IIc+IIa, III). Histologically, tumors were classified into two groups, differentiated (well- or moderately differentiated adenocarcinoma) and undifferentiated (poorly differentiated adenocarcinoma or signet ring cell carcinoma) types. Lymph node metastasis and vessel involvement were examined on bisected planes of each lymph node.

Univariate analysis of liver recurrence risk factors was performed using the chi-square and Mann–Whitney *U* tests. Multivariate analysis was performed using logistic regression analysis. Statistical analysis was performed with SPSS for Windows version 19.0 (SPSS, Chicago, IL, USA). A value of $P<0.05$ was considered to indicate a statistically significant difference.

Table 1 The initial site of recurrence in 48 patients with early gastric cancer

	No. of patients $n=48$
Liver	15 (31)
Lymph node	13 (27)
Bone	8 (17)
Peritoneum	6 (13)
Lung	3 (6)
Local	2 (4)
Lymphangiopathy	1 (2)
Pleura	1 (2)
Ovary	1 (2)
Unknown	1 (2)

Values in parentheses are percentages unless indicated otherwise. In two patients, more than one site was involved at the time of first recurrence

Results

Clinicopathological Features of Patients with Liver Recurrence of EGC

Table 2 shows the clinicopathological features of 15 patients with liver recurrence of EGC as compared to recurrence-free cases. The median age of cases with liver metastasis was 64 years. Twelve were male and 3 were female. The majority of primary tumors had been located in the middle gastric body. Fourteen patients had undergone partial gastrectomy, including pylorus preserving and distal gastrectomies. Macroscopically, nine patients had elevated-type and six depressed-type EGC.

All cases with liver metastasis had shown submucosal invasion. The proportions of differentiated and undifferentiated adenocarcinoma were similar in the two groups. Nodal involvement was found in approximately half of cases with liver metastasis. Lymphatic and vascular involvements were seen in 11 (73%) and 7 (47%) patients, respectively. Thirteen patients (87%) had lymphatic or vascular involvement. Five patients (33%) had both lymphatic and vascular involvement.

The intervals between surgery and detection of EGC recurrence in the liver ranged from 4 to 43 months, with a median of 12 months. Eight patients received chemotherapy and five underwent hepatectomy for liver tumors. The other two patients received palliative care. Three patients who underwent hepatectomy are still alive. The 5-year survival rate of all liver metastasis cases after curative resection was 18.8%.

Analysis of Risk Factors for Liver Metastasis

Univariate analysis revealed that macroscopic type, depth of invasion, lymph node metastasis, and lymphatic and vascular involvements to be significant risk factors for EGC recurrence in the liver. There were no significant differences in other clinicopathological variables between the liver recurrence and recurrence-free groups. All patients with EGC recurrence in the liver had submucosal invasion. None of the patients with mucosal invasion developed liver metastasis. Submucosal invasion was thus determined to be an absolute

Table 2 Clinicopathological features of liver metastasis and recurrence-free groups

	Liver metastasis $n=15$	Recurrence-free $n=2658$	P value
Age (years)[a]	64 (45–72)	61 (21–88)	0.935
Gender			0.231
Male	12	1,795	
Female	3	863	
Location			0.388
U	1	352	
M	12	1,625	
L	2	681	
Gastrectomy			0.371
Total	1	364	
Partial	14	2,294	
Macroscopic type			
Elevated	9	433	
Flat	0	50	0.003
Depressed	6	2,175	
Tumor size (mm)[a]	27(15–105)	30(3–250)	0.907
Depth			<0.001
m	0	1,277	
sm	15	1,381	
Histology			0.464
Differentiated	7	1,343	
Undifferentiated	8	1,315	
Lymph node metastasis			0.001
Positive	7	335	
Negative	8	2,323	
Lymphatic involvement			<0.001
Positive	11	478	
Negative	4	2,180	
Vascular involvement			<0.001
Positive	7	133	
Negative	8	2,525	

Values in parentheses are percentages unless indicated otherwise

[a]Values are median (range)

risk factor for liver metastasis from EGC. Therefore, we focused on risk factors for EGC recurrence in the liver in patients with submucosal tumor invasion, i.e., mucosal cancers were excluded.

Multivariate analysis of patients with submucosal invasion revealed macroscopic elevated type ($p=0.022$) and vascular involvement ($P=0.012$) to be independent predictive factors for liver recurrence of EGC. There were no significant differences in histological type, lymph node metastasis, or lymphatic involvement between patients with and without EGC recurrence in the liver (Table 3).

Discussion

Liver metastasis can be found in 4–13.8% of patients with gastric cancer.[11–15] Previous studies pertaining to EGC recurrence have also shown that the rate of liver metastasis was less than 2%.[2,3,8,16–21] In our study, the rate of liver metastasis is just 0.6% of EGC after curative gastrectomy.

The most commonly accepted theory of metastasis formation is a process consisting of a long series of sequential, interrelated steps.[22] First, primary tumor cells continuously

Table 3 Multivariate analysis of risk factors for liver metastasis in patients with submucosal invasion

	RR	95% CI	P value
Macroscopic type	0.278	0.093–0.831	0.022
Histology	1.471	0.494–4.381	0.488
Lymph node metastasis	1.266	0.393–4.082	0.692
Lymphatic involvement	2.675	0.724–9.893	0.14
Vascular involvement	4.345	1.389–13.589	0.012

RR risk ratio, *CI* confidence interval

proliferate, with accompanying angiogenesis. De-adhesion and invasion of these tumor cells into lymphatic or vascular vessels occurs (intravasation), and the tumor cells thereby enter the circulation. Any tumor cells surviving in the circulatory system eventually become trapped in the capillary beds of distant organs and exit the circulation (extravasation). Upon invading organs, tumor cells grow prolifically with angiogenesis in the metastatic organ (proliferation).[22,23]

In our series, submucosal invasion was an absolute risk factor for liver metastasis of EGC. No case of the liver metastasis from mucosal gastric cancer was found. An understanding of the gastric epithelium microcirculatory system is a basic starting point for elucidating the pathogenesis of EGC metastasis. The gastric mucosal microcirculatory system is characterized by a well-developed true capillary network and long-collecting venules but few lymphatic vessels.[24] Invasion of tumor cells into this system, in particular submucosal layer components including vascular and lymphatic vessels and occasionally lymphoid collections, provides a clue to the mechanism underlying gastric cancer spread in the early phase.[25] Lehnert et al. reported that the risk of lymph node metastasis in gastric cancer with submucosal invasion was four times higher than that in mucosal gastric cancer.[26] To our knowledge, there are only a few liver recurrence cases from mucosal gastric cancer in the literatures.[3,17,18,20] We considered that the liver metastasis from mucosal gastric cancer was extremely rare.

Our results also showed that vascular involvement in the submucosal layer is significantly more important for liver metastasis than nodal and lymphatic involvements. Nodal involvement is recognized as one of the most significant risk factors for early gastric cancer recurrence.[1–8] Indeed, multivariate analysis in our study revealed nodal involvement to be the significant risk for major recurrent sites such as lymph node, bone, and peritoneum except for liver. A significant correlation between liver metastasis of gastric cancer and venous invasion has been reported in several studies.[27–30] Liver metastasis of gastric cancer is generally considered to be caused by invasion of tumor cells via the hematogenous route, especially through the venous system including the portal vein or lymphatic channels, into the systemic circulation. Other investigators have suggested liver metastasis of gastric cancer to occur via a lymphatic route. Kumagai et al. concluded that the lymphatic system is closely related to the establishment of liver metastasis; in particular, extranodal invasion is a significant risk factor for liver metastasis in patients with gastric cancer.[31] Yamagata hypothesized that lymphatico-portal venous anastomosis due to mesenteric lymphatic occlusion was related to liver metastasis. Lymphatico-portal venous anastomosis is reportedly an important factor in the occurrence of liver metastasis of gastric cancer.[32] These reports suggest that cancer development raises the possibility of liver metastasis via various routes and involving complex, perhaps inter-related, phenomena. The results of this study of patients with EGC provided evidence supporting direct invasion of the vascular system by tumor cells as the first step in liver metastasis.

Finally, a macroscopic elevated type tumor was identified as another significant risk factor for liver recurrence in our study. The macroscopic elevated type was a much more common tumor than the depressed-type in the group with liver recurrence of EGC, and this observation might be nonbiased since the majority of cases with pT1 cancers have depressed-type. Elevated type is reportedly one of the risk factors for liver recurrence of EGC.[16,21,33] Kodama et al. suggested that penetrating tumor types with expansive growth are characterized by a dominant elevated lesion, with a relatively high incidence of vessel invasion.[34] In addition, these histological types are closely related to chromosomal instability, i.e., DNA aneuploidy and p53 overexpression, as well as vascular endothelial growth factor activation-induced tumor angiogenesis, vascular invasion, and hematogenous metastasis.[27,35] Our results also indicated that the macroscopic elevated type of submucosal gastric cancer is an independent risk factor for liver metastasis.

In conclusion, patients with mucosal gastric cancer are highly unlikely to develop liver recurrence. Conversely, in submucosal gastric cancer, the presence of vascular involvement and macroscopic elevated-type tumors are associated with liver metastasis. Finally, meticulous follow-up using computed tomography or ultrasonography is essential for patients with the superficial elevated type of submucosal cancer in the presence of vascular invasion, even after radical resection.

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