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ORIGINAL ARTICLE

Intrahepatic micrometastases around liver metastases from gastric cancer

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Abstract
Background/Purpose We aimed to clarify the association between the presence of micrometastases around liver metastases from gastric cancer and the results of hepatic resection. In addition, we investigated the influence of E-cadherin and matrix metalloproteinase (MMP)-7 expression on the development of micrometastases.
Methods Micrometastases around liver metastases were examined microscopically in 31 metastatic liver tumor specimens resected from 17 patients who had undergone hepatic resection for liver metastases from gastric cancer. E-cadherin and MMP-7 expression in the primary gastric tumor, the liver metastases, and the micrometastases were examined immunohistochemically.
Results Hepatic micrometastases were present in around 48% of the liver metastases, accounting for 59% of the patients. The tumor recurrence rate in the remnant liver after hepatic resection was significantly higher, and survival significantly poorer, in patients with such micrometastases than in those without. Micrometastases tended to appear around the liver metastases that had reduced E-cadherin expression. Most of the micrometastases in the lymph ducts and sinusoids showed reduced E-cadherin expression. MMP-7 expression was not correlated with the presence of micrometastases.
Conclusions About half of the hepatic metastases from gastric cancer had seeded off micrometastases, and the presence of these micrometastases was associated with a poorer result of hepatic resection. Reduced E-cadherin expression in metastatic liver tumors may be associated with the development of micrometastases.

Keywords Gastric cancer · Liver metastases · Intrahepatic micrometastases · E-cadherin · MMP-7

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Introduction

Liver metastases are important in primary gastric cancer because they are common and their presence affects prognosis. Although some patients with gastric cancer who present with liver metastases already have metastases elsewhere, hepatic resection is performed in a proportion of patients with gastric cancer liver metastases. However, the usefulness of hepatic resection for gastric cancer liver metastasis, and the indications for resection, remain controversial [1–3].

Intrahepatic micrometastasis is considered to be among the causes of tumor recurrence after hepatic resection for hepatocellular carcinoma [4]. In colorectal cancer liver metastases, the appropriate width of the surgical margin has been discussed in the light of studies of micrometastases [5]. However, the hepatic micrometastasis status of patients with liver metastases from gastric cancer, and its influence on the results of hepatic resection are not known. As the behavior of gastric cancer is not the same as that of colorectal cancer, the two cancers should not be treated in the same way. Although many cancer-related proteins that affect gastric cancer progression and metastasis—such as adhesion molecules and matrix metalloproteinase (MMP)—have been identified, their expression status in liver metastases and their influence on the progression of these metastases is not clear.

We investigated the existence of micrometastases around liver metastases from gastric cancer and its influence on the results of hepatic resection, including the rate of tumor recurrence in the remnant liver. In addition, we assessed the expression status of E-cadherin and MMP-7 and the relationship of this status to the development of associated micrometastases.

Patients and methods

Of the patients with gastric cancer and liver metastases who were treated by curative synchronous or metachronous hepatic resection with gastrectomy between 1991 and 2005, 17 whose resected liver specimens were available for histological examination were enrolled in this study. Hepatic resections were performed in patients whose primary gastric tumors, including lymph nodes, were considered curatively resectable and whose liver metastases were considered curatively resectable by partial to hemihepatic resection in synchronous cases. In metachronous cases, hepatic resections were performed in patients without recurrences at sites other than the liver. Patients with many tumors bilaterally did not receive resection. As a result, the maximum number of resected liver tumors was five. As a rule, hepatic tumors were resected by nonanatomical partial hepatectomy, but anatomical hepatectomy was performed if it was considered safer. The characteristics of the patients and their treatment-related factors are shown in Table 1. There was no fixed regimen of adjuvant chemotherapy after hepatectomy, and selections of each regimen depended on the considerations of the attending surgeons. The clinicopathological classification was in accordance with the Japanese classification of gastric carcinoma, 2nd English edition [6].

Detection of micrometastases around metastatic liver tumors

Of 32 liver metastases resected from the 17 patients with gastric cancer, examination was possible in 31. Formalin-fixed resected liver specimens that included the metastatic liver tumor and surrounding liver tissue were cut to include the tumor's maximum diameter, then one slice was divided into several blocks and embedded in paraffin. Then 4-μm-thick tissue sections from these blocks were stained with hematoxylin and eosin (H&E), and the liver tissue around the metastatic tumor was examined microscopically by one of the authors (T.N.). As a rule, all of the liver tissue around the metastatic tumor was examined, but in 6 tumors a small proportion of the tissue could not be examined. On average, 93.4% of the tissue around each tumor was observed. The broadest width of liver tissue examined around each tumor ranged from 5.5 to 23.0 mm (average 12.2 mm). The narrowest width from the tumor edge to the cut end ranged from 1.0 to 6.0 mm (average 2.7 mm). Micrometastasis around the hepatic metastasis was defined as a cancer cell cluster that had a diameter of 1 mm or less and was separated from the metastatic liver tumor by normal liver parenchyma or separated by at least 1 mm of

Table 1 Patients' characteristics and treatment-related factors

Age (years; average, range)	65.8, 40–79
Sex	
Male	13
Female	4
Temporal relationship	
Synchronous	9
Metachronous	8
Depth	
T1	2
T2	11
T3	3
T4	1
Lymph node metastasis	
N0	4
N1	5
N2	7
N3	1
Number of liver tumors (median, range)	1, 1–5
Lymph node dissection	
D1	1
D2	16
Type of hepatectomy	
Nonanatomical partial hepatectomy	13
Segmentectomy	1
Hemihepatectomy	3
Chemotherapy	
Performed	13
Adjuvant chemotherapy after hepatectomy	10
Systemic	8
S-1	2
UFT	2
5-FU	1
5-FU + CDDP	1
MMC + MTX + 5-FU	1
MMC + 5′-DFUR	1
Hepatic arterial infusion	2
5-FU/CDDP	1
ADM	1
Not performed	4

S-1 tegafur-gimeracil-oteracil-potassium, *UFT* uracil-futrafur, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *MMC* mitomycin C, *MTX* methotrexate, *5′-DFUR* doxifluridine, *ADM* doxorubicin hydrochloride

interstitial tissue. We measured the distance from the edge of the metastasis to the center of the micrometastasis. The location of each micrometastasis was classified as portal vein (PV), lymph duct (LD), hepatic vein, bile duct, sinusoid, or perineural space (PN). LDs were identified by immunohistochemical staining with anti-D2-40 antibody.

Immunohistochemical staining and its assessment

E-cadherin and MMP-7 expression were examined immunohistochemically in 15 primary gastric tumors and 31 metastatic liver tumors and their associated micrometastases, all from the 17 patients mentioned above. Thirty primary gastric tumors without liver metastases but with the same distribution of histological types and depths as in the 15 above-mentioned gastric tumors with liver metastases, were used as controls. We prepared serial sections of each gastric tumor including the deepest layer. We also prepared serial sections of liver tissue next to the sections used in the examination for micrometastases. Anti-human E-cadherin (2 μg/mL, HECD-1; Takara, Otsu, Japan) and anti-hMMP-7 (1:100, 141-7B2; Daiichi Fine Chemicals, Takaoka, Japan) were used as primary antibodies. Four-micrometer-thick tissue sections from paraffin-embedded blocks were dewaxed, dehydrated, and then heated in a microwave oven three times at 900 W for a total of 30 min at 100°C. Endogenous peroxidase was inactivated by incubating the sections with 3% hydrogen peroxide for 20 min. Nonspecific reactions were blocked by incubating the sections in a solution containing 3% skim milk for 10 min. Sections were incubated with primary antibody overnight at 4°C. They were then incubated for 30 min at room temperature with biotinylated anti-mouse and anti-rabbit immunoglobulins, and for 30 min with streptavidin-conjugated peroxidase (LSAB2 System, HRP; Dako, CA, USA). Immunoreaction was visualized by incubation with diaminobenzidine substrate for 5 min. Finally, sections were counterstained with hematoxylin and mounted. As a negative control for MMP-7, sections were processed as above but treated with phosphate buffered saline (PBS) instead of primary antibodies.

E-cadherin expression was assessed in a total of 500 cancer cells in five fields in the invasive area of each primary gastric tumor, and in a total of 500 cancer cells in five fields in the front area of each liver metastasis. We also assessed all the cancer cells in each of the accompanying micrometastases in the liver. Cancer cells that stained similarly to normal epithelium but with accentuation of the cell membrane were judged positive, and those with weak staining intensity or no staining of the cell membrane were judged negative. If 50% or more of the cells were negative, E-cadherin expression in the tumor was considered to be reduced. MMP-7 expression was assessed by counting a total of 500 cells in five representative fields in the invasive front of the primary gastric tumor and the same number in the front area of the liver metastasis; again, we counted all cancer cells in each of the accompanying micrometastases. If 10% or more of the tumor cells showed immunostaining signals, the tumor was considered to express MMP-7.

Liver sections with micrometastases were processed in the same way as above, but were treated with anti-D2-40 antibody (1:100, D2–40; Dako, CA, USA) as the primary antibody. LDs were identified by staining of the endothelial cells.

Results of hepatic resection, and clinicopathological factors

The rate of tumor recurrence in the remnant liver and the survival rate after hepatic resection were estimated by the Kaplan–Meier method. Follow up ranged from 1 to 117 months (median 20 months). Clinicopathological classification was in accordance with the Japanese classification of gastric carcinoma, 2nd English edition [6]. Primary gastric tumors were classified macroscopically as expansive (types 1, 2) or infiltrative (types 3, 4). One superficial tumor that showed IIa + IIc was classified as expansive type. Histological type (differentiated or undifferentiated) was determined in accordance with the classification of Sugano et al. [7].

Statistical analysis

Differences in recurrence and survival rates after hepatic resection were examined by the log-rank test. Fisher's exact test was used to compare E-cadherin and MMP-7 expression in the primary tumor between gastric cancers with and without liver metastases; to check for correlations between E-cadherin and MMP-7 expression in liver metastases and the presence of micrometastases associated with metastatic liver tumors; to compare E-cadherin expression in micrometastases between different locations; and to investigate the correlation between clinicopathological factors and the presence of micrometastases. The JMP IN 5.1.1 statistical analysis software package (SAS Institute, Cary, NC, USA) was used for these analyses.

This study was approved by the Ethics Committee of Yamagata University Faculty of Medicine.

Results

Presence of intrahepatic micrometastases and results of hepatic resection

Ten of the 17 patients (58.8%) who had undergone resection of liver metastases and 15 of the 31 resected hepatic

metastases (48.4%) had micrometastases around the metastatic liver tumors. The number of micrometastases per metastatic liver tumor ranged from 1 to 11 (median 2). The distance from the edge of the liver metastasis to the micrometastasis ranged from 0.3 to 5.0 mm (median 1.1 mm). Nine liver metastases had micrometastases in the PV, 4 had them in the LD, 9 had them in the sinusoid, and 1 had them in the PN. There were no micrometastases in the bile duct or hepatic vein. Histological images of the micrometastases are shown in Fig. 1, and the distribution of the distances from the edge of the liver metastasis to each of all 64 micrometastases, as well as the location of each micrometastasis, are shown in Fig. 2. Fifty-seven of the 64 lesions (89.1%) were located within 2.0 mm of the edge of the liver metastasis.

Mean survival time (MST) in the 17 patients after hepatic resection was 21 months, and the 5-year survival rate was 30.8%. Twelve patients relapsed, 4 patients did not relapse, and in 1 the relapse status was unknown. Seven patients had recurrences in the remnant liver, 4 patients in the lung or brain, 4 in the lymph nodes, and 1 in the peritoneum. The 2-year recurrence rate in the remnant liver was 100% in patients with micrometastases and 28.6% in those without them; this difference was significant ($P < 0.05$; Fig. 3a). The survival rate of patients with micrometastases was significantly worse than that of patients without micrometastases ($P < 0.05$; Fig. 3b). The recurrence rate in the remnant liver in patients with a surgical margin (minimum distance from the edge of the liver metastasis to the cut end of the liver) of less than 5 mm tended to be higher than that in patients with a surgical margin of 5 mm or more ($P = 0.09$; Fig. 4).

Correlation between E-cadherin and MMP-7 expression and the presence of liver metastases and associated micrometastases

E-cadherin expression in the primary gastric tumor was reduced in 11/15 (73.3%) patients with liver metastases and 17/30 (56.7%) patients without liver metastases (controls). MMP-7 was expressed in the primary gastric tumor in 9/15 (60.0%) patients with liver metastases and in 14/30 (46.7%) patients without liver metastases (controls). These differences were not statistically significant.

Figure 5a and b shows immunohistochemical images of liver metastases. Fourteen of the 24 liver metastases (58.3%) with reduced E-cadherin expression had micrometastases around them, whereas only one of the 7 liver metastases (14.3%) with normal E-cadherin expression had such micrometastases ($P = 0.08$). Figure 5c–e shows immunohistochemical images of E-cadherin expression in micrometastases. We examined the relationship between micrometastasis location and E-cadherin expression

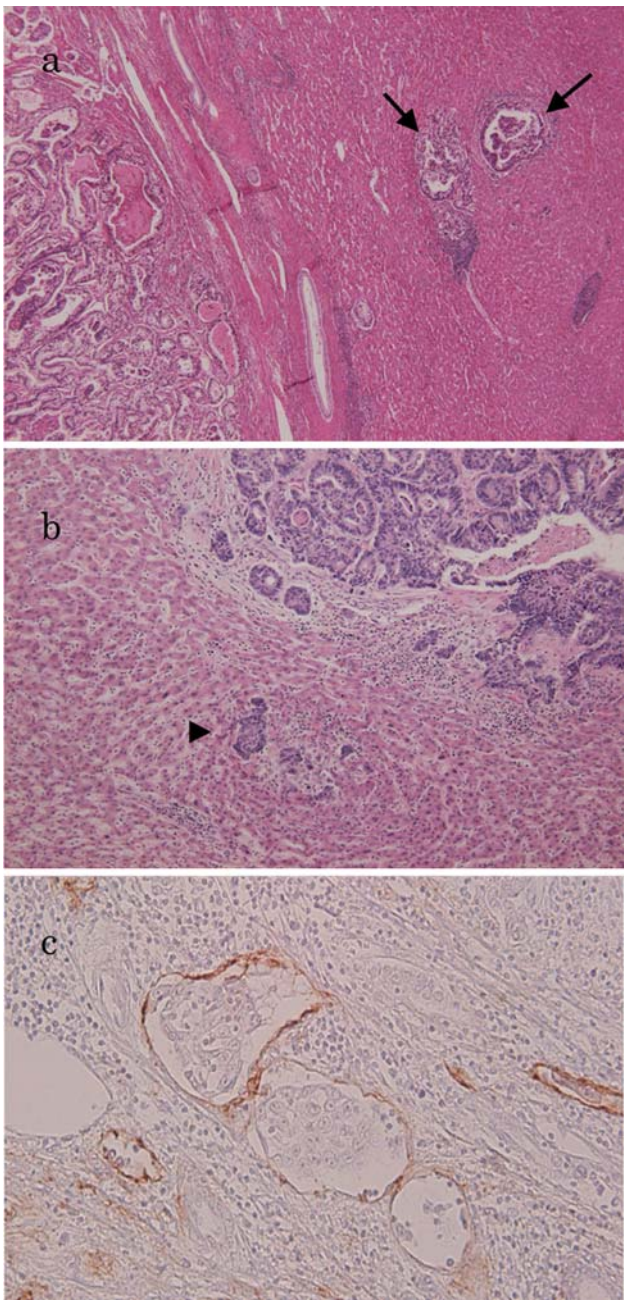

Fig. 1 **a** Micrometastases in portal veins (*arrows*). **b** Micrometastases in a sinusoid (*arrowhead*). **c** Micrometastases in lymph ducts. **a** and **b** H&E, ×40; **c** Anti-D2-40, ×200

(Fig. 6). The proportion of micrometastases with reduced E-cadherin expression was higher in the LD and sinusoids than in the PV. All micrometastases in the sinusoids showed reduced E-cadherin expression.

The incidences of micrometastases around liver metastases with and without MMP-7 expression were 4/13 (30.8%) and 11/18 (61.1%), respectively ($P = 0.15$). MMP-7 expression rates in the micrometastases were 8/32 (25.0%) in the PV, 12/18 (66.7%) in the LD, 2/12 (16.7%) in the sinusoids, and 0/1 in the PN.

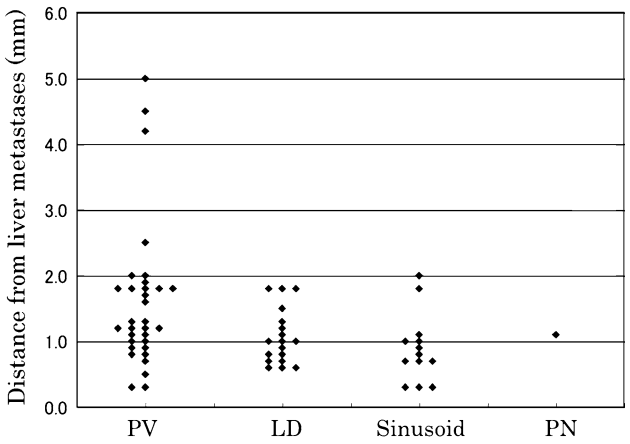

Fig. 2 Distributions of micrometastases according to their locations. *PV* portal vein, *LD* lymph duct, *PN* perineural space

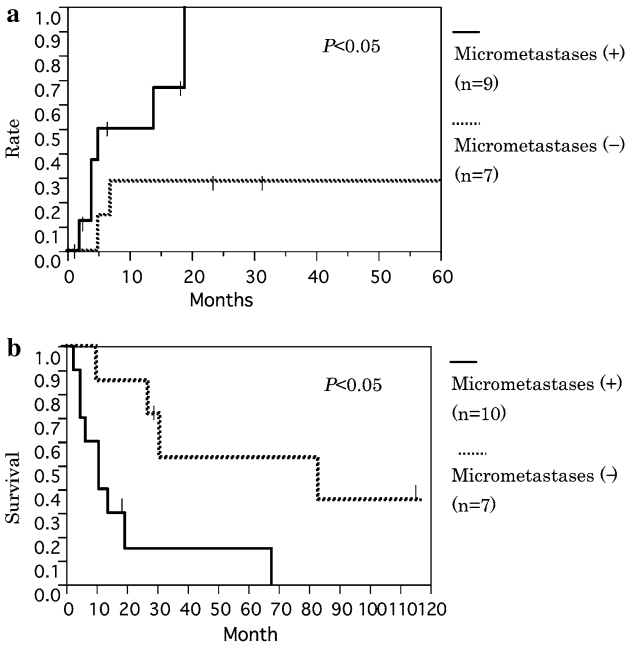

Fig. 3 **a** Recurrence rates in the remnant liver after hepatic resection according to the presence or absence of micrometastases ($P = 0.04$). **b** Survival rates after hepatic resection according to presence or absence of micrometastases ($P = 0.01$)

Correlation between clinicopathology of the primary gastric tumor and liver metastasis and the presence of associated micrometastases

There were no correlations between the presence of micrometastases around liver metastases and the following clinicopathological factors: histological type; size; macroscopic type; depth; lymph node metastases; lymphatic invasion; venous invasion; cancer–stroma relationship; pattern of tumor infiltration into the surrounding tissue of primary gastric tumor; timing of hepatectomy; number of liver metastases; or size of the metastatic liver tumor (Table 2).

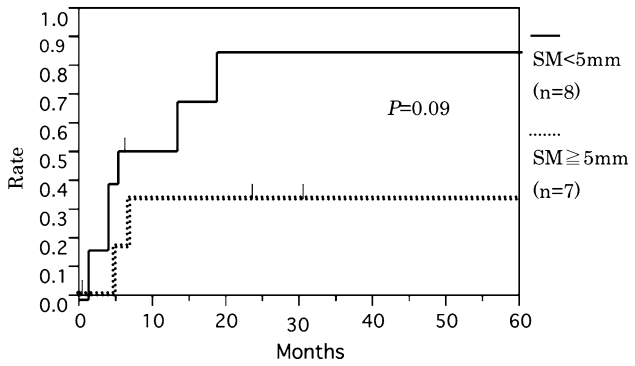

Fig. 4 Relationships of rates and durations of recurrence in the remnant liver after hepatic resection between cases with more than 5 mm in surgical margin (*SM*) and those with less than 5 mm in *SM* (*SM* means minimum distance from the edge of the metastatic liver tumor to the cut end; $P = 0.09$)

Discussion

Micrometastases around metastatic liver tumors were present in 58.8% of patients with gastric cancer metastases in the liver. They were located in the vicinity of the liver metastasis, within 5.0 mm of the tumor border; in patients with micrometastases the recurrence rate in the remnant liver after hepatic resection was high and the survival rate after hepatic resection was poor. Micrometastases tended to be present when E-cadherin expression was reduced in liver metastases, and E-cadherin expression in micrometastases in the sinusoids and LDs was reduced in many patients. Therefore, reduced E-cadherin expression in liver metastases may participate in the development of micrometastasis.

Intrahepatic metastasis is one of the mechanisms of tumor recurrence in the remnant liver in patients with hepatocellular carcinoma [4, 8, 9]. Moreover, recurrence in the remnant liver is the major form of recurrence after hepatic resection in patients with metastatic liver cancer [10–12], but in these patients there are two possible origins of the recurrence: the primary tumor and the initial liver metastases. We often see patients with multiple metastatic liver tumors located in different segments or some distance apart in the same segment; it is therefore reasonable to consider that the recurrences in the remnant liver after hepatic resection for metastatic liver cancer originate from hepatic micrometastases that have seeded from the primary tumor before resection. However, Nanko et al. [13] investigated micrometastases around liver metastases from colorectal cancers and reported that secondary metastasis from metastatic liver tumors was one of the causes of hepatic micrometastasis. This was because the number of

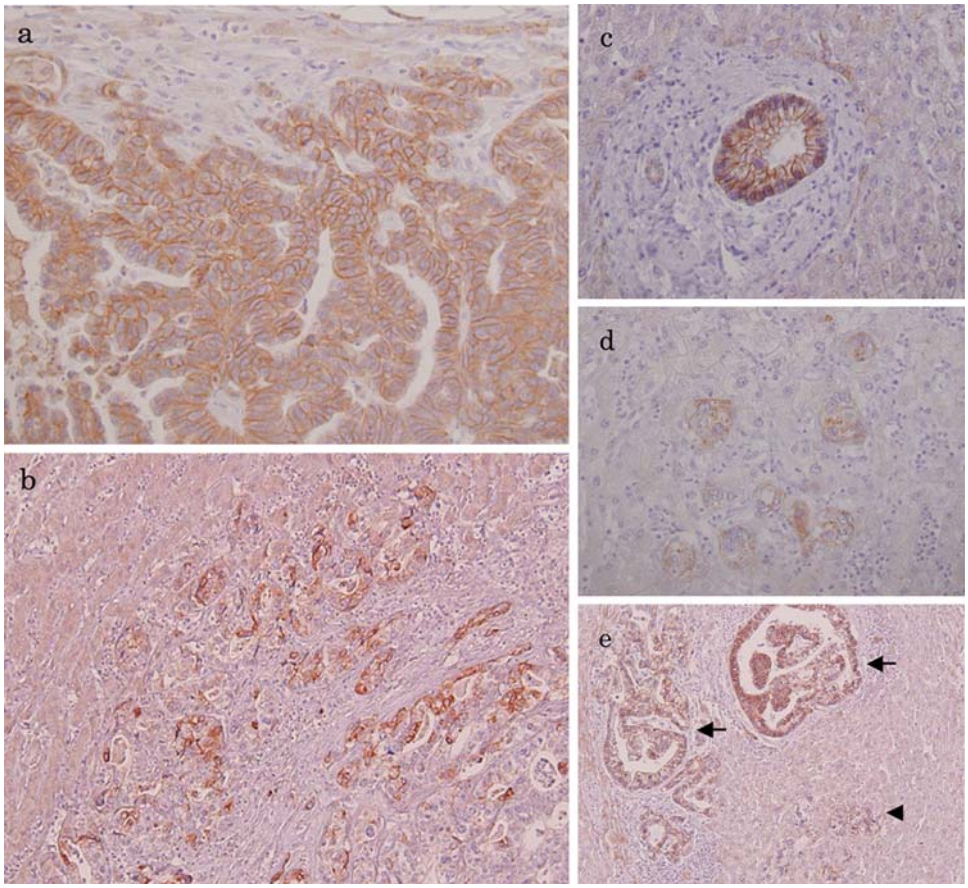

Fig. 5 Histological images of immunohistochemical staining. **a** E-cadherin expression was preserved in the metastatic liver tumor. **b** A metastatic liver tumor shows matrix metalloproteinase-7 (MMP-7) expression. **c** Preserved E-cadherin expression in a micrometastasis in the portal vein. **d** Reduced E-cadherin expression in a micrometastasis in a sinusoid. **e** E-cadherin expression was preserved in a micrometastasis in the portal vein (*arrow*) but reduced in the sinusoid (*arrowhead*) in the same patient. **a**, **c**, **d** ×200; **b**, **e** ×100

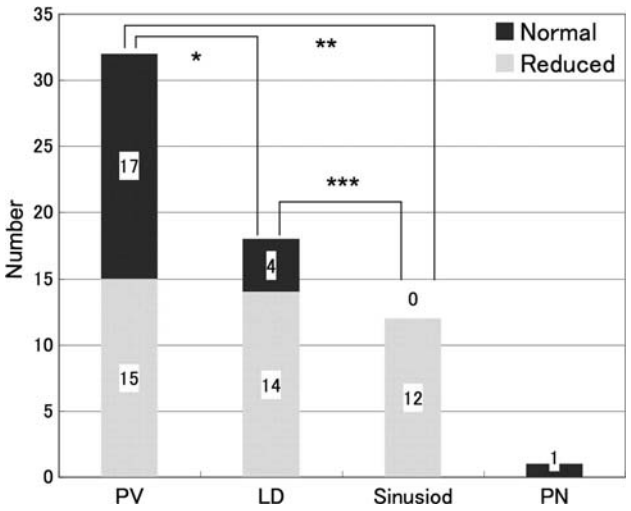

Fig. 6 Status of E-cadherin expression in micrometastases according to their locations. The proportion of micrometastases showing reduced E-cadherin expression was significantly lower in the portal vein (*PV*) than in the sinusoid or in the lymph duct (*LD*). $*P < 0.05$, $**P < 0.005$, $***P = 0.13$. *PN* perineural space

micrometastases became larger, and the distance between the metastasis and the micrometastasis became greater, as the size of the metastasis increased. Yokoyama et al. [14] found a higher rate of recurrence in the remnant liver after hepatic resection in patients with colorectal cancer liver metastases that had micrometastases in surrounding liver tissue than the rate in patients without such micrometastases. These reports suggest that micrometastasis from liver metastases is a mechanism of recurrence in the remnant liver.

Patients with gastric cancer liver metastases tend to have more of these metastases, and to benefit less from their removal, than is the case in patients with colorectal cancer [15]. Therefore, it is reasonable to consider that the influence of micrometastases from the primary tumor on the recurrence rate in the remnant liver after hepatic resection for gastric cancer metastases would be stronger than in colorectal cancer. However, there have been few studies of the status of intrahepatic micrometastases in patients with gastric cancer liver metastases [16]. The prognostic factors in patients who have undergone hepatic resection for gastric liver metastasis have been investigated [1–3], but intrahepatic micrometastasis as a prognostic factor has not been studied.

In our series, the bulk of the micrometastases around metastatic liver tumors were close to the metastatic liver tumors; we therefore considered most of them to have been seeded from these metastases. In a study of micrometastases around metastatic liver tumors in nine patients with gastric

Table 2 Correlation between clinopathological factors and presence of micrometastases around liver metastases

	Micrometastases		*P*
	Present	Absent	
Primary tumor			
Histological type			
Differentiated	8	6	1.0
Undifferentiated	2	1	
Size of tumor			
≥60 mm	4	3	1.0
<60 mm	5	4	
Macroscopic type			
Expansive	4	4	0.63
Infiltrative	6	3	
Depth			
T1, 2	7	5	1.0
T2, 3	3	1	
Lymph node metastasis			
N0, 1	5	3	1.0
N2, 3	5	3	
Lymphatic invasion			
ly0, 1	6	1	0.14
ly2, 3	4	5	
Venous invasion			
v0	6	3	1.0
v1,2,3	4	3	
Cancer-stroma relationship			
Medullary, intermediate	7	5	1.0
Scirrhous	3	1	
INF			
α, β	6	5	0.58
γ	4	1	
Liver metastasis			
Temporal relationship			
Synchronous	6	3	0.64
Metachronous	4	4	
Number of tumors			
Solitary	5	5	0.62
Multiple	5	2	
Size of tumor			
≥25 mm	10	5	0.08
<25 mm	5	11	

INF, Pattern of tumor infiltration into the surrounding tissue

cancer liver metastasis, Isono et al. [16] reported that they were present in 67% of the patients, their maximum distance from the edge of the metastasis was 29.0 mm, and they were located in the PV or hepatic vein, but not in the sinusoids or LD. Their incidence was close to that in the present study, but the maximum distance and location of the micrometastases differed from that in the present series. This discrepancy in distance might have been due to differences in the area of liver tissue observed: we observed the tissue up to a distance of 23.0 mm from each hepatic metastasis. However, it is unlikely that there were many lesions outside the area observed in our series, because about 90% of the lesions we observed were located within 2.0 mm of the edge of the metastasis and no lesion was observed beyond 5.0 mm. In contrast, Isono et al. [16] suggested that a small number of micrometastases were present beyond 5.0 mm. The fact that they studied only a small number of cases might explain the absence of micrometastases in the sinusoids. We were able to identify micrometastases in the LD because of the immunohistochemical staining method, with anti-D2-40 antibody, used in our study.

We found that patients with micrometastases around metastatic liver tumors were liable to suffer recurrences in the remnant liver after hepatic resection, although these micrometastases had been removed by hepatic resection. There are two potential reasons for this: (1) micrometastases from the primary gastric tumor were also present in the remnant liver, because primary gastric cancers with micrometastases around liver metastases have high metastatic potential; and (2) a small number of micrometastases seeded from liver metastases were present outside the resected parts of the liver. If the number of liver metastases in patients with micrometastases were larger than that in patients without micrometastases, then this might have supported the former hypothesis, but we did not find this to be true. On the other hand, recurrence rates in the remnant liver in patients with surgical margins of at least 5 mm tended to be lower than the rates in patients with surgical margins narrower than 5 mm. Ambiru et al. [17] and Miyazaki et al. [3] also reported that surgical margin was a prognostic factor after hepatic resection for gastric cancer liver metastasis. Therefore, we considered that not only metastasis from the primary tumor but also secondary metastasis from metastatic liver tumors was a potential cause of recurrence in the remnant liver.

There was no fixed adjuvant chemotherapy regimen after hepatectomy in the present study. This study included patients treated over a long period, and there was no standard adjuvant chemotherapy even for primary gastric cancer during this period. Many patients received different regimens of adjuvant chemotherapy after hepatectomy depending on the attending surgeons, so that the influences of these chemotherapy regimens on the outcome of hepatectomy were not clear.

Reduced E-cadherin expression in the primary tumor is correlated with metastasis and invasion in gastric cancer [18, 19], and MMP-7 is expressed in gastric cancer cells and acts in their metastasis and invasion [20, 21]. However, there have been many negative reports with regard to the

participation of these molecules in liver metastasis [22–24]. In our series, similarly, the expression status of E-cadherin and MMP-7 was also not correlated with the development of liver metastasis. Elsewhere it has been reported that reduced expression of E-cadherin and increased expression of MMP-7 promote the progression and metastasis of hepatocellular carcinoma [25–27], and that reduced expression of E-cadherin in liver tumors is correlated with prognosis after hepatic resection [28]; it has also been reported that MMP-7 may play an important role in the progression of liver tumors in colorectal cancer metastasis [29]. In our series, micrometastases tended to appear around metastatic liver tumors that showed reduced E-cadherin expression, and the micrometastases themselves in most of the LDs and all of the sinusoids showed reduced E-cadherin expression. In addition, we observed two metastatic liver tumors of which the micrometastases showed normal expression of E-cadherin in the PV, but reduced expression in the sinusoid (Fig. 5e). These findings suggest that the micrometastases in the PV may have been continuous with the liver metastases, and micrometastases in the LDs and sinusoids may have been detached from the liver metastases. MMP-7 expression had no apparent relationship with the presence of micrometastases.

Although the presence of micrometastases around metastatic liver tumors was a factor affecting prognosis after hepatic resection, we can assess this risk only after surgery. We investigated the relationships between the presence of micrometastases and clinicopathological factors, but there were no significant correlations. If the participation of reduced E-cadherin expression in the formation of micrometastases is proved by larger studies, then it may be useful to predict E-cadherin expression in liver metastases by examining E-cadherin expression in the primary gastric tumor.

In conclusion, intrahepatic micrometastases suspected of having been seeded from liver metastases were present in about half of the patients with liver metastases from gastric cancer, and their presence was correlated with poor outcome after hepatic resection. In hepatic resection, surgeons should be aware of micrometastases not only from the primary gastric tumor but also from metastatic liver tumors, and should consider adjuvant therapy in patients with these micrometastases.

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