J. Tokyo Med. Univ., **62**(3) : 314-321, 2004

Overexpression of matrix metalloproteinase-7 (matrilysin) in the involved venous vessel in association with liver metastasis of colorectal cancer

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Abstract

The aim of this study was to investigate the relationship between matrix metalloproteinase-7 (matrilysin, MMP-7) expression patterns and liver metastasis in human colorectal carcinoma. An immunohistochemical analysis for MMP-7 in primary advanced colorectal cancer was performed on 32 patients with synchronous liver metastasis (group S), 30 patients with metachronous liver metastasis (group M), and 33 control patients who had neither synchronous nor subsequent liver metastasis and survived with a disease-free course for more than 5 years after surgery (group C). Basement membrane laminin staining was used to distinguish the small involved lymphatic vessels from the small involved veins. There was no significant clinicopathologic difference between the liver metastasis groups and the control group. The expression rates of MMP-7 were: 84.4% (group S), 80% (group M) and 66.7% (group C) at the invasive margin ; 81.3% (group S), 73.3% (group M) and 36.4% (group C) in the involved lymphatic vessels ; and 82.8% (group S), 70.3% (group M) and 13.8% (group C) in the involved veins. At the invasive margin, there was no significant difference in MMP-7 expression rates among the three groups. But both in the involved lymphatic vessels and in the involved veins, the expression rates of MMP-7 were significantly higher in the liver metastasis groups than in the control group ($p<0.01$, $p<0.0001$, respectively). Overexpression of MMP-7 in the involved lymphatic vessels, and particularly in the involved veins seems to be predictive of liver metastasis in colorectal cancer.

Introduction

In the metastatic process, cancer cells first break out through their basement membrane, invade through the surrounding stroma into local lymphatic vessels and capillaries, and then break out of the vascular structures at distant sites to establish new tumors[1,2)]. Colorectal cancer is one of the most common gastrointestinal cancers. Liver metastasis is the major cause of death in colorectal cancer patients, and it is estimated that liver metastasis develops in 75% of patients who die of colorectal cancer[3)]. Some investigators reported that liver metastasis of colorectal cancer correlated with several histopathological findings including growth pattern[4)], venous invasion[5)], lymph node metastasis[6)] and with molecular biological proteins such as p53 and vascular endothelial growth factor (VEGF)[7)]. However, these factors have rarely been utilized in clinical work, because of their low specificity in identifying liver metastasis. Proteolytic degradation of the extracellular matrix

Received January 20, 2004, Accepted February 20, 2004
Key words : Matrix metalloproteinase-7, Tumor invasion, Liver metastasis, Colorectal carcinoma
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(ECM) by matrix metalloproteinases (MMPs) is an important part of the tumor invasive and metastatic process[1,2]. Of MMPs, MMP-7 (matrilysin), the smallest MMP member, is known to be expressed predominantly by cancer cells themselves and plays a crucial role in tumor invasion and metastasis[8-10]. Immunohistochemical studies have shown that MMP-7 expression is frequently observed at the invasive margin and correlates with tumor progression in various tumors[11-13]. Yamashita et al.[14] reported that the MMP-7 expression was located in carcinoma cells and correlated with lymph node and liver metastases in human gastric carcinomas. In colorectal cancer, some authors reported that the expression of MMP-7 at the invasive margin is significantly related to lymph node metastasis, tumor stage or poor prognosis[15-17], however, there has been no definite assessment about the correlation between MMP-7 expression patterns in primary tumors and liver metastasis. We found in the present study that MMP-7 expression either in the involved lymphatic vessels or in the involved veins was significantly higher in liver metastasis patients than in control patients. To identify patients at high risk of developing liver metastasis, using laminin staining to distinguish lymphatic capillaries from blood vessels[18,19], we retrospectively investigated the relationship between MMP-7 expression in the involved lymphatic vessels or in the involved veins and liver metastasis in primary advanced colorectal cancer.

Patients and Methods

Patients and tissue samples

Paraffin-embedded tumor specimens from 95 patients with advanced colorectal cancer[20] were used for immunohistochemical analysis. Prior informed consent was obtained from each patient before surgery. All patients had undergone resection at Tokyo Medical University Kasumigaura Hospital between January 1993 and January 1998, and had received neither chemotherapy nor radiation therapy before surgery. The patients were classified into the following three groups: 32 patients with synchronous liver metastasis (group S), 30 patients with metachronous liver metastasis (group M) and 33 control patients who had neither synchronous nor subsequent liver metastasis and survived with a disease-free course for more than 5 years (group C). Metachronous liver metastases were detected by computed tomography (CT) or magnetic resonance imaging (MRI) during follow-up. Clinicopathological features of tumors including location, size, gross type, histology, depth, lymphatic invasion, venous invasion and lymph node metastasis were classified according to the Japanese classification of colorectal carcinoma[20].

Immunohistochemistry

In this study, paraffin sections of 4-μm in thickness were immunostained with monoclonal antibodies for MMP-7 (141-7B2, 10 μm/ml, Fuji Chemical, Toyama, Japan) by the Envision +/HRP method with heat-induced antigen retrieval. The sections were deparaffinated and heated to 99°C in a microwave oven (650 W) for 20 min to retrieve the antigen. The endogenous peroxidase activity was suppressed by a solution of 3% hydrogen peroxide in methanol for 15 min. After being rinsed three times in phosphate-buffered saline (PBS), the sections were incubated with monoclonal antibody against MMP-7 for 2 hours at room temperature. Then the sections were treated with goat antimouse immunoglobulins conjugated to peroxidase labeled-dextran polymer (K4001, Dako, Carpinteria, CA, USA) for 1 hour. After washing in PBS, the sections were developed in 0.05 M Tris-HCl buffer containing 0.6 mg/ml 3, 3′-diaminobenzidine tetrahydrochloride (DAB) for 6 min. The nuclei were counterstained with Mayer's hematoxylin. By omitting the primary antibody, negative control sections were stained.

Using continual paraffin sections, staining for the basement membrane component laminin (Z0097, 5 μm/ml, Dako, Glostrup, Denmark) was performed to distinguish lymphatic capillaries from small veins by the same immunohitochemical method. As well, the sections were treated with proteinase K (S3004, 20 mg/ml, Dako, Japan) for 5 min to retrieve the antigen. The secondary antibody complex used goat anti-rabbit immunoglobulins conjugated to peroxidase labeled-dextran polymer (K4002, Dako, Carpinteria, CA, USA).

Evaluation of immunostaining

Immunopositive cell area was used for evaluation of the staining of MMP-7 antibody. Immunopositive cell rates were calculated at the invasive margins, in the lymphatic invasions and in the venous invasions, respectively. Cases with MMP-7 positive expression at the invasive margin were considered when immunopositive cell rates were more than 30% of cancer cells, as described previously by Yamamoto et al.[11], and cases with MMP-7 positive lymphatic or venous invasions were judged when the immunopositive cell rate in one of the involved vessels was more than 30% of cancer cells. In all sections the basement membranes of endothelial cells, normal glands, smooth muscle cells and peripheral nerves were stained for laminin.

Statistical analysis

All analyses were carried out using StatView-J 5.0 statistical software (SAS Institute Inc, Cary, NC, USA). The statistical significance of clinicopathological features and the expression of MMP-7 among the three groups were determined by the chi-square test, Bartlett test and Kruskal-Wallis rank test. A P value of less than 0.05 was considered to indicate a statistically significant

difference.

Table 1 Comparison of clinicopathologic features among three groups

Variables	groups			*P* value
	S (n=32)	M (n=30)	C (n=33)	
Age				
mean±S.D.	67.4±9.4	66.8±11.0	63.0±9.9	0.6815[a]
Sex				
male	22	18	24	0.5489[b]
female	10	12	9	
Location				
colon	18	17	23	04515[b]
rectum	14	13	10	
Tumor size				
≦4 cm	13	12	17	0.5780[b]
>4 cm	19	18	16	
Gross type				
1	2	1	3	0.8155[b]
2	16	16	19	
3	14	13	11	
Depth				
mp	1	3	5	0.8769[c]
ss-se	22	19	18	
si	9	8	10	
Histology				
wel	4	6	7	0.8679[b]
mod	23	21	22	
muc+por	5	3	4	
Lymphatic invasion				
positive	29	24	25	0.3758[b]
negative	3	6	8	
Venous invasion				
positive	27	23	23	0.3739[b]
negative	5	7	10	
Lymph node metastasis				
positive	23	18	20	0.5390[b]
negative	9	12	13	

[a]: Bartlett test, [b]: Chi-square test, [c]: Kruskal-wallis rank test, S.D.: Standard deviation.

Results

Comparison of clinicopathological features among the three groups

In our study, lymphatic or venous invasions were evaluated by negative or positive (minimal, moderate, severe)[20]. We compared the clinicopathological features among the three groups, and found no significant differences in age, sex, tumor location, tumor size, gross type, tumor depth, histologic type, lymphatic invasion, venous invasion, or lymph node metastasis (Table 1). Based on laminin staining, the intensity of basement membrane staining was weaker and more focal in lymphatic vessels than in blood vessels (Fig. 1A), then we distinguished lymphatic invasions from venous invasions. Meanwhile, the involved vessels were more frequently observed when compared with hematoxylin-eosin (H & E) staining, the lymphatic invasions were detected in all patients, and the patients with venous invasion were: 29/32 in group S, 27/30 in group M and 29/33 in group C. According to laminin staining, there was also no significant difference in lymphatic invasion or venous invasion among the three groups (Table 2).

Comparison of MMP-7 expression among the three groups

The cytoplasm and cell membrane of carcinoma cells were diffusely stained for MMP-7, but no MMP-7 staining was found in normal gland epithelial cells or stromal cells. Neither normal nor tumor cells showed positive staining in negative control sections. The distributions of MMP-7 were frequently located at the lumenal surface of neoplastic glands in deeply invading areas, particularly at the invasive margin (Fig. 1B). Controlling with laminin staining, MMP-7 positive tumor cells in the involved lymphatic vessels and in the involved veins were frequently observed in the invasive margin and subserosa but few in the submucosa (Fig. 1C, D, E and F), and in particular, micro-metastases in small lymphatic vessels or in small veins were frequently stained strongly for MMP-7 (Fig. 1G). We detected MMP-7 expression at the tumor invasive margin, in the involved lymphatic vessels and in the involved veins. The expression rates of MMP-7 were: 84.4% (27/32, group

Fig. 1 Immunostaining for laminin and MMP-7 in colorectal cancer tissues.
A: Staining for laminin, lymphatic vessels showing weak, thin or focal positive reaction for the besement membrane of endothelial cells (→). Small veins showing strong, thick linear positive reaction for the basement membrane of endothelial cells and smooth cells (➡). Peripheral nerves also showing positive staining for laminin (▲). (×100)
B: MMP-7 positive staining at the invasive margin. (×40)
C: MMP-7 positive staining in the involved lymphatic vessel. (×400)
D: Laminin staining for this involved lymphatic vessel showing weak and focal basement menbrane staining (→). (×400)
E: MMP-7 positive staining in the involved vein. (×100)
F: Laminin staining for this involved vein showing strong and dense besement menbrane staining (➡), although the partial wall of this vein was destroyed by tumor cells. (×100)
G: Micro-metastasis showing strong MMP-7 staining in the small involved vein. (×400)

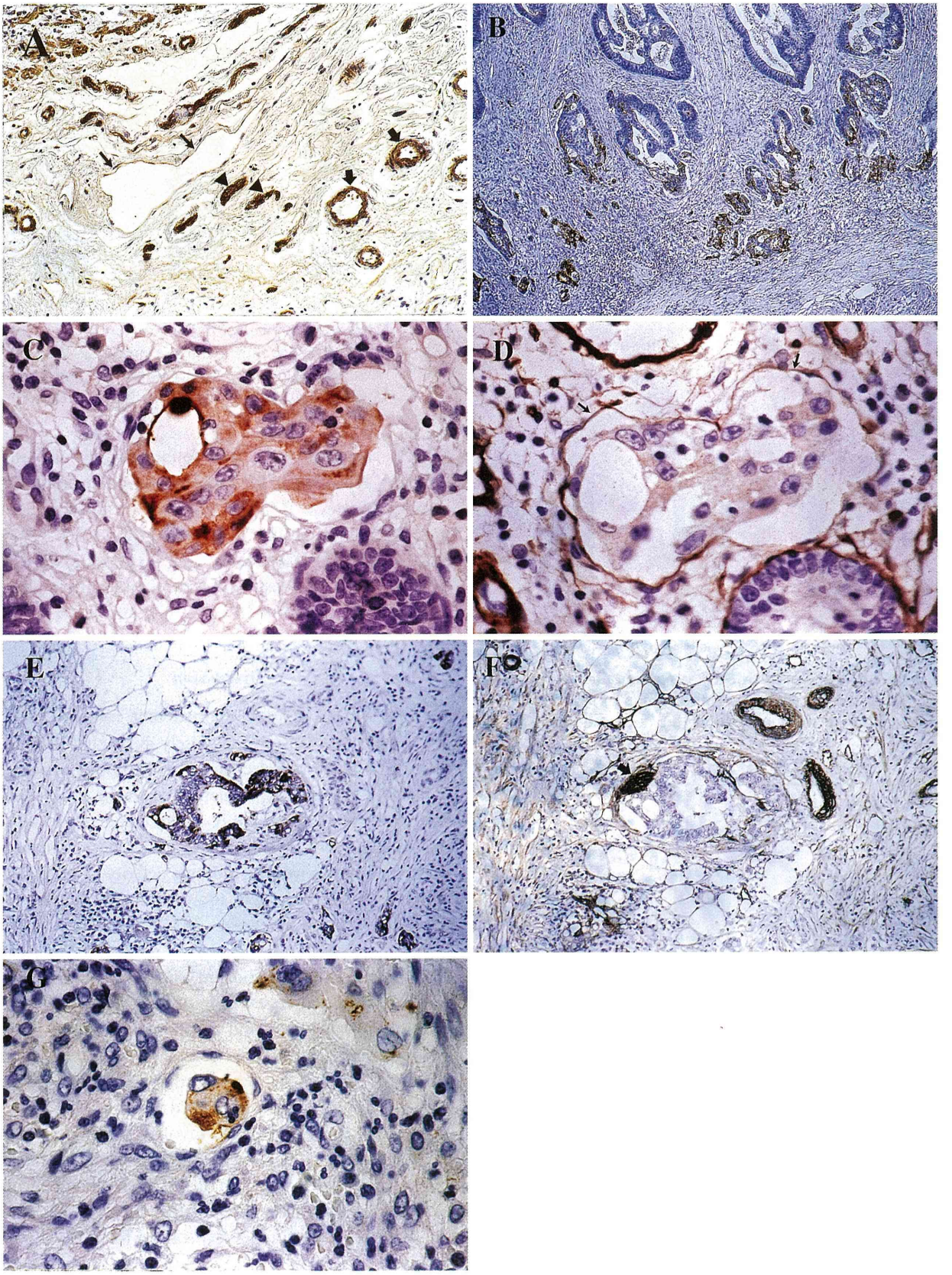
A
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Table 2 Comparison of the incidence of lymphatic invasion and venous invasion evaluated by laminin staining among three groups

Variables	Laminin staining			*P* value
	S (n=32)	M (n=30)	C (n=33)	
Lymphatic invasion				
positive	32	30	33	NS
negative	0	0	0	
Venous invasion				
positive	29	27	29	0.5390[b]
negative	3	3	4	

[b]: Chi-square test, NS: not significant.

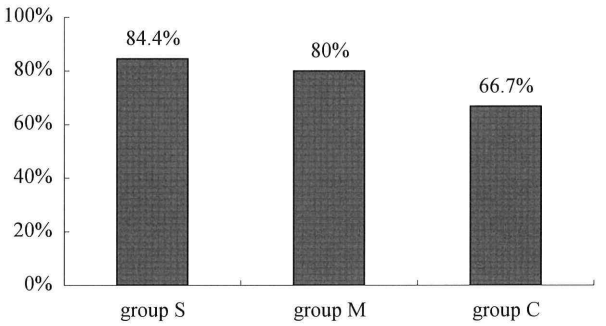

Fig. 2 Comparison of the MMP-7 expression rates at the invasive margin among the three groups. No significant difference was found among the three groups.

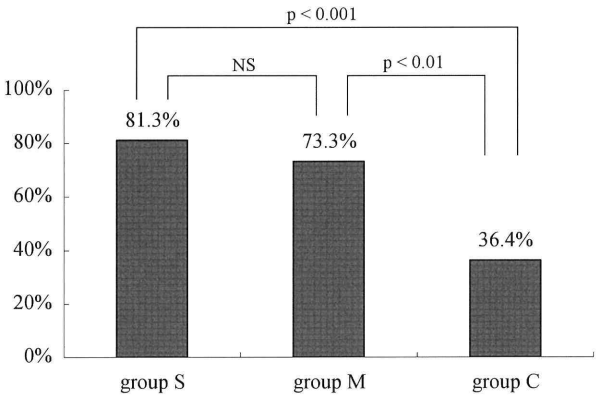

Fig. 3 Comparison of the MMP-7 expression in the involved lymphatic vessels among the three groups. The MMP-7 expression rates were significantly higher in group S and in group M than in group C ($p<0.001$, $p<0.01$). NS: not significant.

S), 80% (24/30, group M) and 66.7% (22/33, group C) at the tumor invasive margin (Fig. 2) ; 81.3% (26/32, group S), 73.3% (22/30, group M) and 36.4% (12/33, group C) in the involved lymphatic vessels (Fig. 3) ; and 82.8% (24/29, group S), 70.3% (19/27, group M) and 13.8% (4/29, group C) in the involved veins (Fig. 4). At the invasive margin, no significant difference in

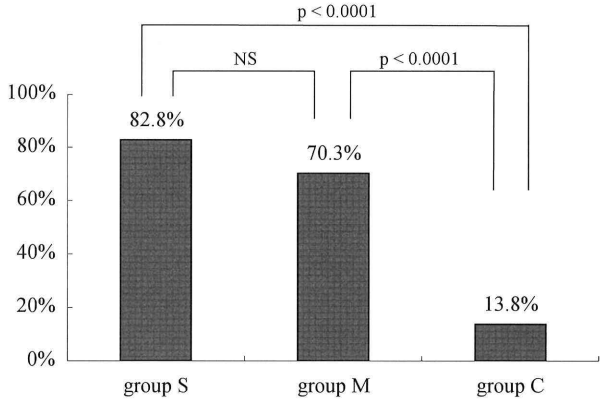

Fig. 4 Comparison of the MMP-7 expression in the involved veins among the three groups. The MMP-7 expression rates were significantly higher in group S and in group M than in group C ($p<0.0001$). NS: not significant.

MMP-7 positive rates was found among the three groups. However, in the involved lymphatic vessels, the expression rates of MMP-7 were significantly higher in group S and in group M than in group C ($p=0.0002$ and $p=0.0033$). Moreover, the expression rates of MMP-7 in the involved veins were significantly higher in group S and in group M than in group C ($p<0.0001$ and $p<0.0001$).

Discussion

Some clinical studies reported that venous invasion and lymphatic invasion are closely associated with liver metastasis in colorectal cancer[5,6]. Although venous or lymphatic invasion is frequently observed in advanced gastrointestinal cancers, only a very small percentage of circulating tumor cells finally develops into liver metastasis[21]. To discover the biologic activity of tumor cells which can establish new tumors in distant sites is a notable focus of research. MMP-7 has the highest activity against insoluble elastin which is the highly cross-linked ECM component of elastic connective tissues such as blood vessels[22], indicating that MMP-7 may promote intravasation and extravasation of tumor cells by degrading the vascular basement membrane in the metastatic process. In our study, we focused on the MMP-7 expression in the involved vessels. The MMP-7 expression rates either in the involved lymphatic vessels or in the involved veins were significantly higher in the liver metastasis groups than in the control group. Furthermore, we detected that the micro-metastases in the small veins were frequently stained for MMP-7 in the liver metastasis groups. The patients with MMP-7 positive micro-metastases had an earlier liver recurrence time and worse outcome than those without (data not shown). Our results suggest that this MMP-7 expression pattern plays a critical role in the development of liver metastasis. Mori et al.[23] and Ishikawa et al.[24]

reported that MMP-7 mRNA is significantly higher in liver metastases than in adjacent normal liver tissues and in primary tumors, emphasizing the important role of MMP-7 production and activation in liver metastasis formation of colorectal cancer. Other studies also showed that MMP-7 induced angiogenesis in vivo[25], and resisted apoptosis in vivo by modulating signaling through the Fas pathway[26], implying that MMP-7 positive tumor cells may have an ability of establishing new tumors in distant sites. MMP-7 positive expression is frequently located in the tumor cell clusters at the tumor invasive margin, however, in the control group, most of the venous invasions were located in the submucosa, and the degree of venous invasions was either minimal or moderate but severe (data not shown). Furthermore, only in one case was found with micro metastases in vein at the invasive margin. These findings may be possible clinicopathological reasons why MMP-7 positive tumor cells markedly decreased in the control group. Meanwhile, an in vitro study showed that MMP-7 expression is regulated by nuclear β-catenin in human colorectal cancer[27]. Ougolkov et al.[16] also found a significant correlation between nuclear β-catenin and MMP-7 expression at the tumor invasive front in patients with metastatic colorectal cancer. These results indicate that nuclear β-catenin may be one of important molecules of inducting MMP-7 activation in tumor progression.

Some authors reported that the MMP-7 mRNA levels were positively expressed in about 90% of colorectal cancer cases[23,28]. It is thought that MMP-7 expression at the invasive margin may be an essential factor of facilitating tumorigenicity and local invasion. Though MMP-7 expression at the invasive margin was described to correlate with tumor stage[15-17], in our study, there was no significant difference in MMP-7 expression at the invasive margin between the liver metastasis groups and the control group. When tumor cells invade into vessels and still maintain the ability of producing MMP-7, they may have a potential of developing into distant metastasis.

Laminin staining for the basement membrane was reported to be useful for separating lymphatic capillaries from blood vessels[18]. Inada et al.[19] also used laminin staining to identify small involved veins which were not recognized by Victoria blue /hematoxylin-eosin (VB-HE) double staining. In our study, comparing with routine H & E staining, laminin staining method was more sensitive to detect the involved vessels. Although the incidence of either lymphatic invasion or venous invasion was no significant difference between the liver metastasis groups and the control group, the MMP-7 expression in the involved vessels seems to be a reliable predictive marker of liver metastasis. It may be feasible to use immunohistochemical analysis of MMP-7 in routine clinicopathologic work to identify high-risk patients and to choose an appropriate postoperative therapy after curative surgery of colorectal cancer.

In conclusion, the MMP-7 expression rates in the involved lymphatic vessels, and particularly in the involved veins were significantly higher in the liver metastasis groups than in the control group. These expression patterns of MMP-7 may be useful in predicting liver metastasis of colorectal cancer.

Acknowledgements

The authors thank Mr. Tsutomu Kohda for technical assistance, and thank Prof. J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this manuscript.

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大腸癌における MMP-7 の発現と肝転移予測の検討

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【要旨】　病理組織学的に同じ進行度でも、癌浸潤、転移の程度が異なっていることについて、様々な研究がなされている。今回、大腸癌の局所浸潤及び脈管内への侵入に関連する MMP-7 の発現は臨床的に肝転移予測に有用なパラメーターとなり得るかを検討するため、1993 年から 1998 年に当科切除された大腸癌症例中、同時性肝転移群 (S 群) 32 例、異時性肝転移群 (M 群) 30 例、術後 5 年間肝転移無再発症例 (C 群) 33 例を対象し、MMP-7 に対する特異抗体を用いて Envision＋方法にて免疫組織学的染色を行った。静脈管及びリンパ管の判定は Laminin 染色を用いた。結果としては、三群の間に臨床病理学的な差が認められなかった。浸潤先進部で MMP-7 の発現率は S 群 27/32 (84.4%)、M 群 24/30 (80%)、C 群 22/33 (66.7%) と三群の間に有意差が認められなかったが、リンパ管内 MMP-7 の発現率は S 群 26/32 (81.3%)、M 群 22/30 (73.3%)、C 群 12/33 (36.4%) で、静脈管内 MMP-7 の発現率は S 群 24/29 (82.8%)、M 群 19/27 (70.3%)、C 群 4/29 (13.8%) で、肝転移群と対象群間に有意差が認められた ($p<0.01$、$p<0.001$)。静脈管内及びリンパ管内での MMP-7 発現は臨床的に肝転移予測の有用なパラメーターと示唆られた。陽性症例に対して、術後の積極的な集学的治療が必要と考えられた。

〈**Key words**〉　MMP-7、脈管侵襲、肝転移、大腸癌