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Tumor Vascular Microenvironment of Colorectal Hepatic Metastasis and Chemotherapy Response

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Abstract. *Background: The tumor vascular microenvironment has an important role in tumor progression and metastasis. The objective of this study was to assess the significance of metastatic hepatic tumor vascular microenvironment in relation to the response to systemic fluorouracil-based chemotherapy [folinic acid/fluorouracil/oxaliplatin (FOLFOX) or folinic acid/fluorouracil/irinotecan (FOLFIRI)]. Patients and Methods: A total of 48 consecutive patients with colorectal cancer (CRC) with hepatic metastasis were retrospectively reviewed, and factors such as metastatic tumor vascular microenvironment, chemotherapy response and hepatic resection, were analyzed. Tumor angiogenesis was microscopically evaluated by microvessel density (MVD) in sections stained immunochemically with antibody to CD34 in patients with hepatic resection. Angiogenesis in the tumor microenvironment in association with ring enhancement (RE) on computed tomography (CT) was also examined. Results: Microscopic examination revealed that peripheral RE on CT of the metastatic tumor was associated with tumor angiogenesis by MVD. The overall response rate after six courses of first-line chemotherapy for liver metastasis with RE on CT was 64% (23/36), whereas the response rate for those without RE was 25% (3/12), which was significantly lower, although the survival of patients with RE-positive and RE-negative tumors did not differ significantly. Conclusion: Peripheral RE of metastatic hepatic tumor on CT was associated with angiogenesis in the tumor microenvironment and higher chemotherapy response.*

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Colorectal carcinoma (CRC) is one of the most common types of cancer. Approximately 50% of patients develop liver metastases at some point during their disease course (1-3). Patients who are candidates for surgical resection of their liver metastases can expect a prolonged survival or even cure (4, 5). However, only 10 to 25% of patients are candidates for liver resection (6, 7). In patients with unresectable metastases, chemotherapy is the treatment of choice, and although it is often used with palliative intent, it may also be used in an attempt to render the metastases resectable (8, 9). Chemotherapy can also be administered as a neoadjuvant treatment for selected cases of resectable metastasis (10). Thus, most patients receive chemotherapy.

Angiogenesis is an essential process in many physiological and pathological conditions, including embryonic development, organ regeneration, chronic inflammation, and tumor growth and metastasis (11, 12). Metastatic liver tumors express factors such as vascular endothelial growth factor (VEGF), which is a well-known angiogenic growth factor. The amount of this angiogenic factor affects survival of patients with metastatic disease (13). In the tumor microenvironment, newly formed angiogenic vessels supply metastatic tumors with nutritional blood and growth factors, which leads to tumor proliferation, growth, and survival.

Imaging, such as computed tomography (CT), is generally used to monitor response to chemotherapy according to the new guidelines for response evaluation (RECIST criteria) (14). Complete response (CR) is usually defined as the disappearance of target lesions on imaging and is considered a good indicator in the evaluation of the efficacy of chemotherapy. The correlation between imaging and pathological status is not well defined. Whether radiological features, including radiological CR, are correlated with pathological features, including complete pathological response, is important for the management of patients.

We examined the significance of tumor peripheral ring enhancement (RE) on contrast CT of hepatic metastases from

CRC regarding the response to first-line systemic chemotherapy. Furthermore, the correlation between the radiological and pathological status, including angiogenesis in the tumor microenvironment, was investigated in patients who underwent resection of their initial liver metastasis.

Patients and Methods

Between 2006 and 2015, data of 48 consecutive patients treated for liver metastasis from CRC were collected prospectively. The treatments were performed at the Department of Gastrointestinal Surgery at Yamanashi University Hospital between 2006 and 2009 or at the Department of Surgery at Tsuru Municipal Hospital between 2010 and 2015. The study was approved by the Institutional Review Board (approval no. 202005). Informed consent was obtained from all patients.

No patients with synchronous liver metastasis simultaneously underwent resection of both the primary and secondary metastatic lesions. All patients first underwent surgery for the primary tumor. Open colectomy was performed in 29 patients and anterior resection of the rectum was performed in 16 patients, including two cases of transient colostomy because of cancer ileus. Three patients underwent Mile's operation. After the initial operation, adjuvant systemic chemotherapy following the 5-fluorouracil (5-FU)-based regimen, as described in the systemic chemotherapy section, was started within 1 month in cases of synchronous metastatic disease. In patients without confirmed hepatic metastasis, prophylactic systemic chemotherapy was not performed. Twelve cases of (metachronous) hepatic metastasis were found during the follow-up period. After confirmation of newly formed hepatic metastasis, adjuvant systemic chemotherapy was started. Adjuvant chemotherapy was performed for all patients with hepatic metastasis as systemic disease to prevent surrounding invasion or distant metastasis and to increase resectability. Hepatic resection was conducted excluding inoperable multiple bi-lobular deposits of the liver and/or systemic disease such as lung metastasis or peritoneal dissemination.

Systemic chemotherapy. Most patients in this series (n=48) were treated using a chemotherapy regimen based on 5-FU/leucovorin combined with oxaliplatin [mFOLFOX6 (15)] or with irinotecan [FOLFIRI (16)]. The following first-line chemotherapy regimens were administered before liver metastases disappeared: 39 patients received mFOLFOX6 and three patients received mFOLFOX6 plus bevacizumab; five patients received FOLFIRI and one patient received FOLFIRI plus panitumumab, for a total of 48 patients (Table I). Second-line chemotherapy was used in cases of disease progression after first-line chemotherapy. Radiological response to systemic chemotherapy was assessed according to RECIST criteria (14).

Imaging. Triple-phase helical CT with 5-mm reconstruction (TOSHIBA TSX-101A; TOSHIBA, Tokyo, Japan) and abdominal ultrasound (TOSHIBA Nemio SSA550A, Xario SSA660A; TOSHIBA) was performed for all patients before chemotherapy and after every six cycles of chemotherapy. Scans of the liver were acquired with 16× (0.75-mm collimation and pitch of 1.356), and were subsequently reconstructed at 3-mm intervals. Settings were 200 mA and 120 kV. Nonionic contrast medium (Omnipaque; Daiichi Pharmaceutical Co, Ltd, Tokyo, Japan) was injected at a rate of 3 ml/s (2 ml/kg) by an MCT power injector. Arterial-phase abdominal images were obtained 35 s after injection and portal-phase images were obtained at 80 s. Although colorectal liver metastasis was visualized better on the portal venous phase, tri-phasic CT was performed systematically for the evaluation of colorectal metastasis to improve the CT readings. All CT images were reviewed independently by radiologists. The CT images were compared with previous CT images. Abdominal angiography was also performed *via* a femoral approach by radiologists for some patients (17).

For quantitative analysis of CT images, regions of interest (ROI) were selected on the basis of the best tumor image on the portal phase of contrast-enhanced CT. Tumor peripheral RE was assessed as follows: The ROI in the peripheral RE area was measured by at least five independent enhanced spot areas as a CT value in Hounsfield units (HFU). The CT value of normal liver parenchyma was also measured in an area near to the tumor without tumor-altered vascularity. The mean CT value was used, and the difference in the CT values between the RE area and the normal liver parenchyma was defined as the RE CT value (Figure 1A). The cut-off value dividing patients into RE-positive and -negative groups was defined as 5 HFU.

Tumor microenvironment vascularity by pathological and immunohistochemical examination. Resected specimens of liver samples were fixed in 10% formalin and embedded in paraffin. Thin sections were deparaffinized twice with xylene and rehydrated in a series of ethanol solutions. Sections were placed in 0.01 mol/l trisodium citrate dehydrate buffer (pH 6.0) and treated in a microwave oven for 10 min at 500 W.

For CD34 staining, tissue sections were digested with 0.2% trypsin in 0.01 mol/l phosphate-buffered saline for 20 min at 37˚C. The tissues were immersed in 3% H_2O_2 with distilled water for 10 min to inactivate endogenous peroxidases. After blocking nonspecific binding by normal goat serum, sections were incubated overnight at 4˚C with mouse monoclonal antibody to CD34 (1:25; QB-END/10, Novocastra Laboratories, Newcastle, UK) as the primary antibody. This was followed by reacting with biotinylated anti-immunoglobulin and labeling using streptavidin-biotin reaction kit peroxidase (Dako, Carpinteria, CA, USA). The peroxidase reaction was visualized with 0.01% H_2O_2 and 3,3'-diaminobenzidine under light microscopy (200× magnification). Microvessel density (MVD) was used to evaluate the microscopic tumor angiogenesis in colorectal liver metastases (18). For MVD after CD34 staining, the average number of stained vessels was calculated using the five most peri-tumor vascular areas in the 14 metastatic liver cancer lesions examined at 200× magnification (Figure 2).

Patient management and follow-up. Preoperative systemic chemotherapy was continued postoperatively for six to eight cycles except in cases of grade 3 or 4 toxicity. Patients were followed up every 3-4 months during the first 2 years and every 6 months thereafter. At each follow-up visit, tumor recurrence was assessed by clinical examination and liver ultrasound. Abdominal and chest CT was performed every 3-6 months. All surviving patients were followed-up for a minimum of 12 months after surgery.

Statistics. Quantitative data are expressed as the mean and standard deviation (SD). Quantitative and qualitative variables were compared using the Fisher's exact test or the Mann-Whitney *U*-test as appropriate. Overall survival (OS) in both metachronous and

Table I. *Chemotherapy regimens used in the study.*

	No. of patients (%)	RE status on CT, n (%)		*p*-Value*
		RE+	RE–	
mFOLFOX6	39 (81)	28 (78)	11 (92)	
mFOLFOX6+Bev	3 (6)	4 (11)	0 (0)	
FOLFIRI	5 (11)	3 (8)	1 (8)	
F0LFIRI+P-mab	1 (2)	1 (3)		0.59

Bev: Bevacizurnab; P-mab: panitumumab. *Comparing RE-positive and -negative tumors.

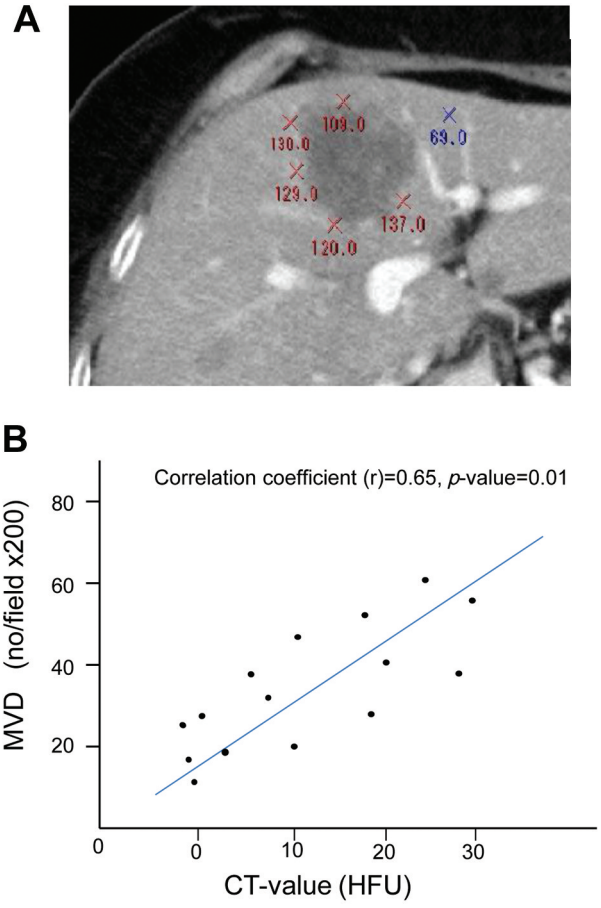

Figure 1. *A: Quantitative analysis of computed tomography (CT) findings. The regions of interest (ROI) were selected based on the best tumor image on contrast-enhanced CT. The ROI of the peripheral ring enhancement (RE) area was measured at at least five independent enhanced spots (red cross) as a CT value in Hounsfield units (HFU). The mean CT value was used, and the difference in the CT value between the RE area and liver parenchyma (blue cross) was defined as the RE CT value. B: The relationship between the microvessel density (MVD) and CT value. MVD was measured using a CD34-stained specimen and CT values were measured at the peripheral RE area as described in the PMx Patients and Methods section.*

synchronous cases was defined as the period from the day of starting systemic chemotherapy at the development of metastatic hepatic tumors to the day of death from any cause. The OS rate was calculated using the Kaplan–Meier method and the log-rank test was used to assess the OS differences between groups. Significance was defined by a value of $p<0.05$.

Results

Patients and tumor characteristics. Clinical and tumor characteristics of 48 patients with liver metastases are shown in Table II. Of these 48 patients, 36 had synchronous metastatic disease and 12 had metachronous disease. The mean age of patients at the time of diagnosis was 66.2±12 years (range=38-82 years). Primary cancer included colon carcinoma in 29 patients and rectal carcinomas in 19. TNM classification (19) was as follows: T1-T2 in two and T3-T4 in 46. There was lymph node involvement in 38 patients. Pathological diagnoses included well-differentiated adenocarcinoma in 27, moderately differentiated adenocarcinoma in 20, and mucinous adenocarcinoma in 1. The mean number of liver metastases was 4.8 (range=1-12). Distant metastases excluding hepatic metastases were observed in 11 patients with lung metastasis on preoperative CT examination. Peritoneal dissemination was confirmed in seven patients by surgical exploration.

Thirty-six patients had synchronous hepatic metastasis. Thirty-one synchronous cases were initially treated by resection of the primary lesion followed by systemic chemotherapy, and six patients eventually underwent liver resection. The other 30 patients were not considered for resection of the liver metastases for the following reasons: Inoperable multiple bi-lobular deposits of the liver and/or systemic disease such as lung metastasis or peritoneal dissemination. Two patients initially underwent diversion colostomy for colon obstruction. After confirmation of a good chemotherapy response, the primary lesion was removed.

Twelve out of 48 patients had metachronous hepatic metastasis. Metachronous hepatic metastasis was defined by a hepatic tumor found longer than 12 months after the initial treatment. There were eight resectable metastatic liver tumors and four inoperable cases. Hepatic resection was eventually performed in 14 patients, comprising 42 lesions. The operative procedures included hemihepatectomy (n=2), segmentectomy or sectionectomy (n=6), and partial resection (n=21). Additional ablation therapy by radiofrequent ablation was performed in 10 patients.

Clinical tumor characteristics of patients with liver metastases according to RE status on CT are summarized in Table II. There was no significant difference between the two groups regarding the clinical characteristics except for pathological diagnosis.

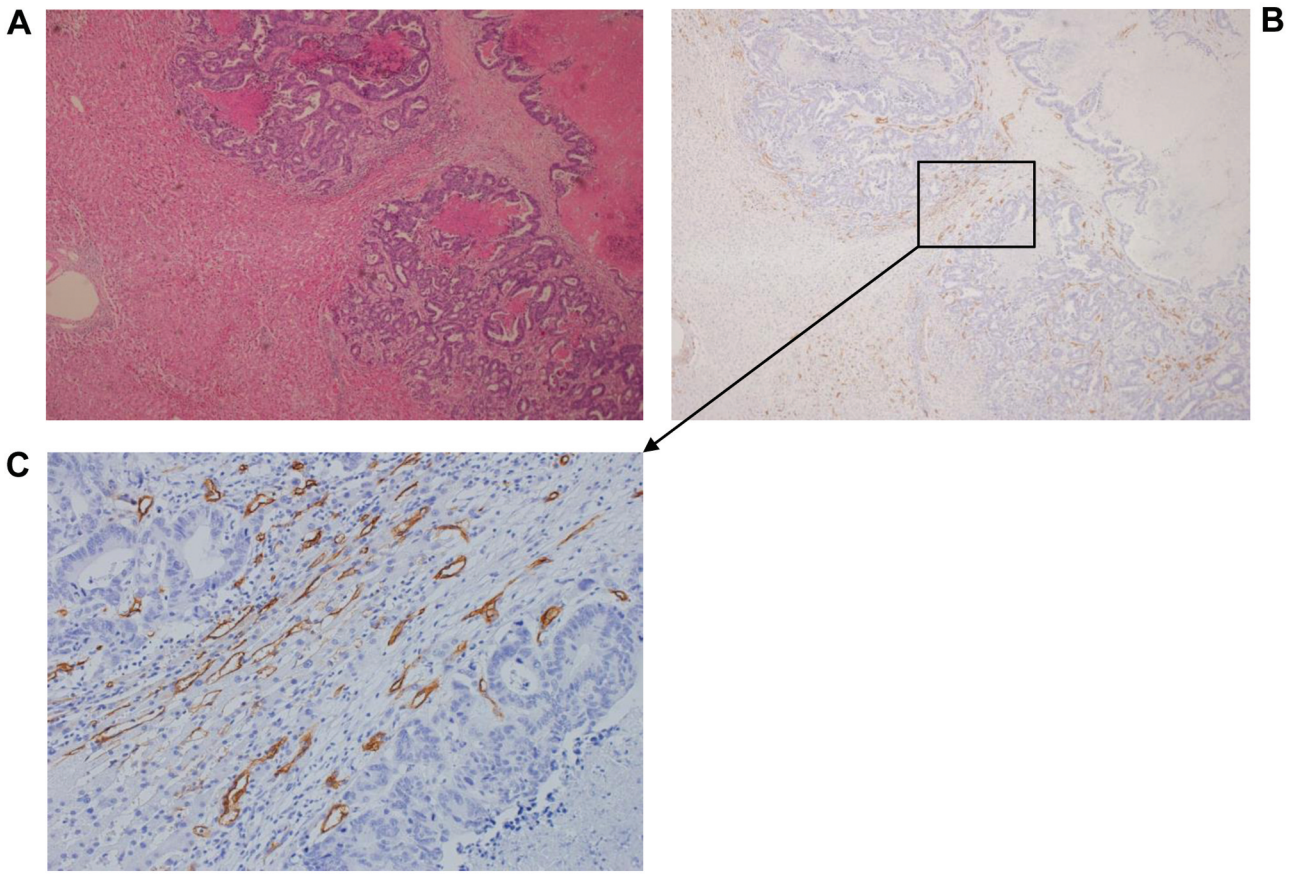

Figure 2. *Microscopic examination of a resected hepatic metastatic tumor. CD34 was stained as described in the Patients and Methods section. A: Microscopic view (40× magnification) of the metastatic hepatic tumor revealed moderately differentiated tubular adenocarcinoma. B: CD34 staining is shown at low magnification (40×). Inset shown in B at high magnification (200×).*

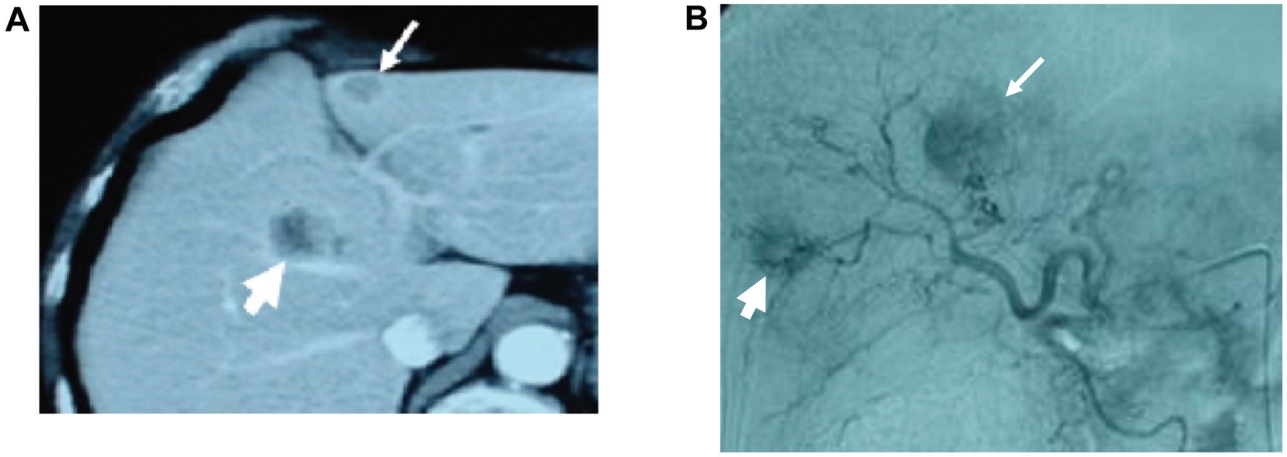

Figure 3. *A: Metastatic hepatic tumors from colorectal cancer exhibiting ring enhancement on computed tomography (CT) (arrows). B: Selective angiography from the common hepatic artery. Thick and thin arrows on the CT images correspond to thick and thin arrows on angiography.*

Table II. *Clinical and tumor characteristics of patients with multiple liver metastases.*

Characteristic	Subgroup	Overall	RE status on CT		*p*-Value*
			+	–	
Gender, n (%)	Male	32 (67)	26 (72)	6 (50)	0.06
	Female	16 (33)	10 (28)	6 (50)	
Age, years	Mean±SD	66.2±12	67±12	64±12	0.20
Primary cancer, n (%)	Colon	29 (60)	22 (61)	7 (58)	0.50
	Rectum	19 (40)	14 (39)	5 (42)	
T-Stage, n (%)	T1-T2	2 (4)	2 (6)	0	0.55
	T3-T4	46 (96)	34 (94)	12 (100)	
N-Stage, n (%)	N1-N2	38 (79)	29 (80)	9 (75)	0.58
Pathological diagnosis, n (%)	Well	27 (56)	21(58)	6 (50)	0.03
	Mod	20 (42)	14(39)	6 (50)	
	Muc	1 (2)	1 (3)	0	
Metastasis at diagnosis, n (%)	Synchronous	36 (75)	28 (76)	8 (73)	0.56
	Metachronous	12 (25)	9 (24)	3 (27)	
No. of liver lesions	Mean±SD	4.8±3	5±2	4±2	
M Status, n (%)	M0	37 (77)	27 (75)	10 (83)	0.44
	M1	11 (23)	9 (25)	2 (17)	
P Status, n (%)	P0	41 (85)	32 (89)	9 (75)	0.47
	P1	7 (15)	4 (11)	3 (25)	

CT: Computed tomography; M Status: metastasis to another organ; Mod: moderately differentiated adenocarcinoma; Muc: mucinous adenocarcinoma; P Status: metastasis to peritoneum; RE: ring enhancement; Well: well-differentiated adenocarcinoma. *Comparing RE-positive and -negative tumors.

Initial chemotherapy response. Overall chemotherapy responses are shown in Table III. The total response rate was 54% (26/48), including two with CR and 24 with partial response (PR). Chemotherapy responses separated by metastatic hepatic tumor with and without peripheral RE are indicated in Table III. The chemotherapy response rate of patients with RE-positive tumors was 64% (23/36) and of those with RE-negative tumors was significantly lower at 25% (3/12). The disease control rate (CR+PR+stable disease/CR+PR+stable disease+progressive disease) of those with RE-positive tumors was 86% (31/36) and of RE-negative tumors was 75% (9/12).

Table III. *Tumor response to chemotherapy according to ring enhancement (RE) on computed tomography (CT).*

Response	Overall	RE status on CT, n	
		Positive	Positive
CR/PR, n	2/24	23	3
SD/PD, n	14/8	13	9
Total, n	48	36	12
ORR	54% (26/48)	64% (23/36)*	25% (3/12)*
DCR	83% (40/48	86% (31/36)	75% (9/12)

CR: Complete response; DCR: disease control rate; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease. *$p<0.05$, Fisher's exact probability test.

Quantitative analysis of angiogenesis in the tumor microenvironment and RE of metastatic hepatic tumors. Tumors with peripheral RE on contrast-enhanced CT (Figure 3A) corresponded to round, stained tumors on abdominal angiography (Figure 3B), suggesting the identification of RE of hepatic metastatic lesions due to newly formed blood flow.

Histopathological and immunostaining examination of a metastatic hepatic tumor is shown in Figure 2. A microscopic view of the metastatic hepatic tumor revealed moderately differentiated tubular adenocarcinoma (Figure 2A). The surrounding tissues, including sinusoidal tissue, hepatocytes, fibroblasts, and endothelial cells, were compressed and invaded by the metastatic hepatic tumor. CD34 staining is shown in Figure 2B and C. CD34-stained cells were observed in host liver parenchyma, including compressed sinusoidal tissues, and invaded into metastatic cancer tissues. Small vessels formed from CD34-stained endothelial cells were growing.

Quantitative analysis of the CT findings for MVD is shown in Figure 1. MVD was associated with the RE CT-value of the metastatic hepatic tumor, revealing a strong positive relationship between microscopic tumor angiogenesis and the peripheral metastatic tumor RE (correlation coefficient=0.65, $p=0.01$). The metastatic tumor peripheral RE on CT may reflect angiogenesis of the tumor.

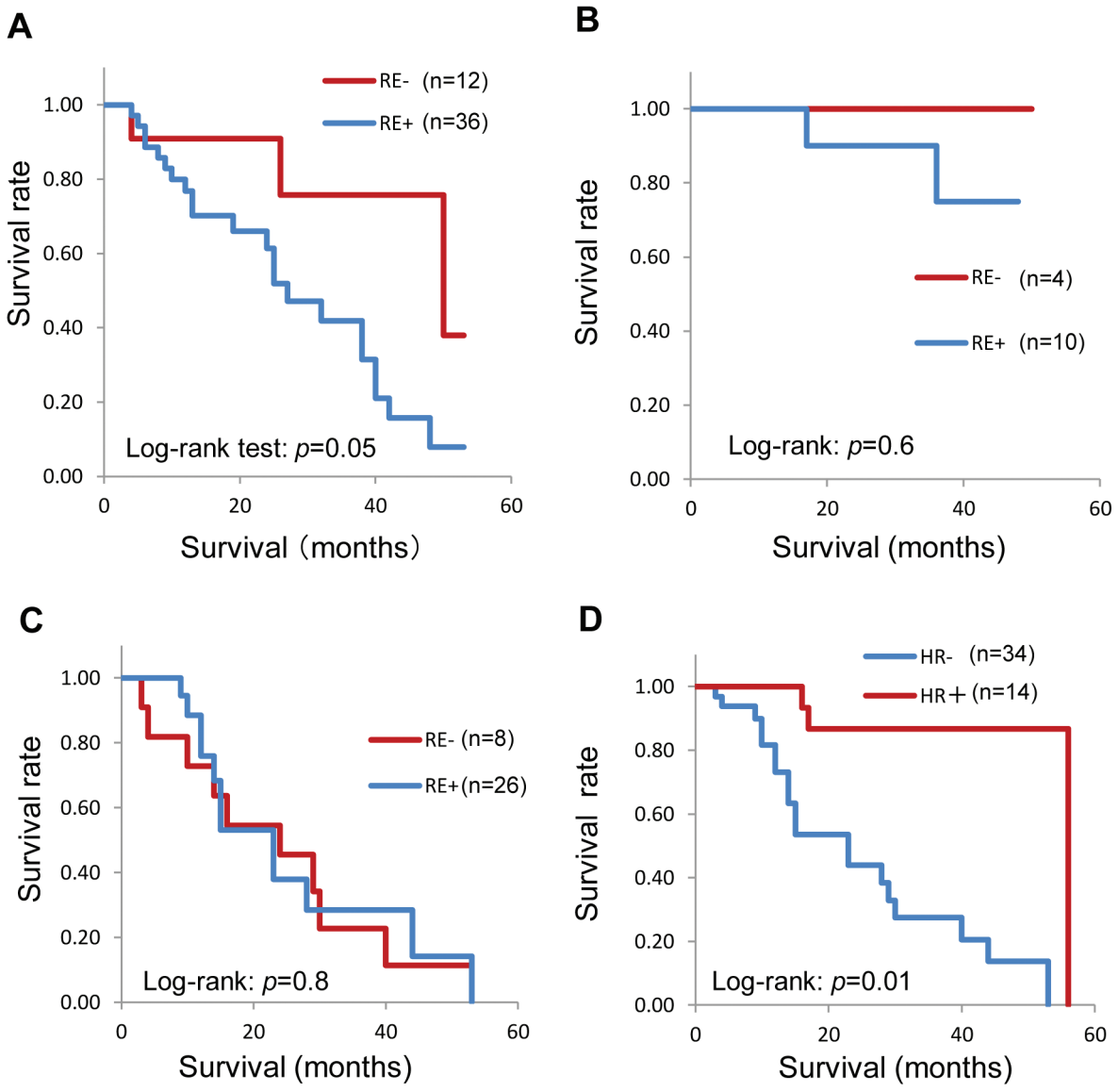

Figure 4. *A: Overall survival (OS) in the whole cohort of patients according to ring enhancement (RE). B: OS of patients who underwent hepatic resection according to RE. C: OS in patients who did not undergo hepatic resection according to RE. D: OS in patients with (HR+) and without (HR−) hepatic resection.*

OS of patients according to RE. The curves for OS after systemic chemotherapy of patients are shown in Figure 4. The OS considering the whole patient cohort did not significantly different between those with RE-positive tumors and those with RE-negative tumors (Figure 4A). The mean OS of patients with RE-positive tumors was 28.1 months and that of those with RE-negative tumors was 43.0 months (p=0.05). The OS curves of patients with RE-positive or -negative tumors who underwent hepatic resection is shown in Figure 4B. There were no significant differences between the groups: The mean OS of patients with RE-positive tumors was 42.1 months and that of those with RE-negative tumors was 48.0 months (p=0.6).The OS of patients with RE-positive or -negative tumors who did not undergo hepatic resection was also not significantly different (Figure 4C) at 25.8 and 23.7 months, respectively (p=0.8). Survival was observed to be longer in the group which underwent hepatic resection than in that which did not (Figure 4D).

Discussion

We found that the peripheral RE on CT of metastatic hepatic tumors is associated with the angiogenesis in tumor microenvironment and may predict a good chemotherapy

response. The combination of liver resection with chemotherapy improved the survival of patients who had multiple hepatic metastases. There are several reports on the concept of peripheral RE on CT of CRC metastasis (20-23). CT-based morphological criteria, including peripheral rim of enhancement of hepatic metastatic tumors, was reported to have a strong association with the pathological response and survival. Our findings partly support these studies.

Angiogenesis is associated with tumor aggressiveness and poorer prognosis in patients with hepatic tumors (24, 25). Tumor angiogenesis facilitates metastatic formation by providing mechanisms to increase the likelihood of tumor cells invading the blood circulation, and provides nutrients for tumor growth and survival at the metastatic site. The interaction of tumor cells with endothelial cells in the tumor microenvironment has an essential role in tumor angiogenesis. Blood nutrient supply and tumor-related endothelial cells promote tumor cell proliferation and tumor growth (26). The tumor microenvironment is essential for the formation of a newly metastatic lesion. Tumor cells and host cells, such as endothelial cells or fibroblasts, participate in tumor metastasis. Tumors that are not vascularized at the metastatic site are typically maintained as small dormant nodules, and the tumor volume remains constant because of a balance between cell proliferation and cell death. Thus, tumor growth is dependent on angiogenesis.

We assessed clinical angiogenesis of metastatic hepatic tumors using indirect imaging by enhanced CT. The clinical manifestation of peripheral RE on CT of metastatic hepatic tumor was confirmed to correspond with tumor angiogenesis on abdominal angiography (Figure 3). This is supported by the investigation of the correlation between angiographically assessed vascularity and blood flow in hepatic metastases from colorectal carcinoma (22). Of note, the hemodynamics of contrast medium between abdominal angiography and enhanced CT images were different. Angiography images were taken in the direct celiac arterial phase, whereas enhanced CT images were taken in the indirect portal phase through the intravenous injection of contrast medium. However, there was a possibility that tumor staining on angiography and peripheral RE on CT was the same because both images may reflect newly formed angiogenic vessels.

There are several methods to monitor angiogenesis using conventional imaging such as contrast-enhanced ultrasound, CT, and magnetic resonance imaging. Enhanced CT is frequently used in the clinical setting, and can readily access metastatic hepatic tumors and surrounding tissues. Contrast-enhanced CT is useful for evaluating tumor angiogenesis by immunohistochemical quantification of the MVD in patients with colorectal adenocarcinoma (23). Evaluation of angiogenic vessels showed the MVD is associated with microscopic tumor angiogenesis (18). We found a strong relationship between microscopic tumor angiogenesis and peripheral metastatic tumor RE on CT.

Hepatic tissue including hepatocytes is fed by blood from the portal vein or hepatic artery, and the blood supply drains *via* the hepatic vein. Metastatic hepatic tumors may be supplied through angiogenesis *via* the portal vein or arterial blood flow. Metastatic hepatic tumors were reported to have a dual blood supply from both the portal vein and hepatic artery (27, 28). In our study, clinical angiogenesis was able to be assessed not only by peripheral RE on portal-phase CT, but also by arterial flow on celiac angiography. This suggests that metastatic hepatic carcinoma is fed from dual blood flow from the portal vein and hepatic artery. Therefore, the clinical manifestation of RE on CT of the metastatic hepatic tumor may be closely associated with tumor angiogenesis.

Angiogenic hepatic metastatic tumors responded well to systemic chemotherapy despite their aggressiveness. Angiogenic tumors may readily uptake anticancer drugs through newly formed angiogenic vessels. Furthermore, immature angiogenic vessels are fenestrated (29). Angiogenic factors, such as VEGF, which was first identified as a vascular permeability factor (30, 31), not only stimulate endothelial cells lining nearby microvessels to proliferate and migrate, but also render these vascular endothelial cells hyperpermeable. Hyperpermeable vessels may readily leak plasma proteins and deliver anticancer drugs into the extravascular space.

Recent clinical anti-angiogenic therapies, such as angiogenic antibody, have been used in patients with unresectable metastatic hepatic disease (32, 33). Anti-angiogenic antibody therapy itself is insufficient for anticancer effects. However, a single infusion of anti-VEGF reduced tumor perfusion, vascular volume, MVD, interstitial fluid pressure, and circulating endothelial cells in patients with rectal cancer (34). This suggests that anti-angiogenic therapy has direct antivascular effects on human tumors. A combination of these drugs with anticancer drugs produces anticancer effects. Anti-angiogenic molecules, such as anti-VEGF, remodel tumor-related endothelial cells into normal endothelial cells with a normal structure (35, 36). Anti-angiogenic molecules reshape pathological vasculature into normal vasculature, which results in delivery of anticancer drugs to tumor. Although we analyzed only a few patients using anti-angiogenic agents in this study, there were antitumor effects without anti-angiogenic agents. Anti-angiogenic therapy may not be associated with a direct tumor response, but rather maintenance of antitumor effects. Normalization of tumor-related vasculature may enable the sustained delivery of anticancer drugs.

Hepatic resection remains the only potential curative treatment for metastatic tumors and improves survival (37, 38). In accordance with this, we found that resection of metastatic hepatic tumors improved OS (Figure 4D). When the groups were divided by hepatic resection, there were no significant differences between patients with RE-positive and those with RE-negative tumors in those who underwent hepatic resection (Figure 4B). In addition, there were no significant differences

between patients with RE-positive and -negative tumors in those without hepatic resection (Figure 4C). A higher response rate to systemic chemotherapy was observed in patients with RE-positive tumors, but the OS rate of patients with RE-positive tumors was not significantly different from that of patients with RE-negative tumors (Figure 4A). This suggests that a higher response to systemic chemotherapy does not always lead to longer survival. After the initial higher response in our patients, additional surgical therapy prolonged survival. To improve survival, additional therapeutic strategies, such as maintenance chemotherapy, use of molecular targeted drugs, or immuno-checkpoint inhibitors, are needed. Clinically, hepatic metastatic tumors can recur or develop other metastatic lesions, such as a lung metastases or peritoneal dissemination, during the follow-up period for RE-positive and -negative tumors, which may affect patient survival.

There were a few limitations in the present study. Firstly, there were patients without clinical manifestations, such as lung metastasis or peritoneal dissemination, during the initial treatment period. Secondly, the statistical power was weak because the sample size was small. The observational period of 10 years was relatively long, but new molecular drugs, such as anti-VEGF and anti-epidermal growth factor receptor, were not frequently used for the initial treatment. Further studies with a larger number of patients and a shorter time period are needed to confirm our results.

Conclusion

We found that tumor peripheral RE on contrast CT in metastatic hepatic tumors from CRC was correlated with angiogenesis in the tumor microenvironment and indicated a good response to recent 5-FU-based systemic chemotherapy.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

HO, SS, HI and HW participated in the operation or management of the patients in this study. HO conducted the majority of the analysis and wrote the article. All Authors read and approved the final article.

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