Hepatic blood flow by perfusion computed tomography as an imaging biomarker for patients with gastric cancer

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Abstract. Perfusion computed tomography (PCT) is a less invasive imaging modality that provides information about tissue hemodynamics at the capillary level. The present study aimed to investigate the correlation between hepatic perfusion and gastric cancer progression. A total of 136 patients with gastric adenocarcinoma were evaluated in the present study. Prior to initial treatment, liver PCT was performed across the hepatic hilar plane and the hepatic blood flow (HBF) was measured using the dual-input deconvolution method. HBF was compared with clinicopathological factors, patient prognosis and circulating serum proangiogenic cytokines. The median HBF was 217 ml/min/100 g tissue. Patients with high HBF had larger tumors (43 mm vs. 71, P<0.001) and more advanced tumor-node stages (P<0.001 for both). When both patient groups of operable and inoperable were compared by their respective median HBF values, each high-HBF group had a significantly worse prognosis (P=0.002 and P=0.024), notably in the inoperable group, with <1-year survival. In 17 postoperative recurrent patients, the high-HBF at recurrence group also had a significantly worse postrecurrent prognosis (P=0.019). HBF was an independent prognostic factor (hazard ratio, 2.019; P=0.048) and was strongly associated with serum vascular endothelial growth factor level (R=0.607, P<0.001). HBF was significantly correlated with gastric cancer progression, and is an easily measured imaging biomarker reflecting patient survival.

Introduction

Locally advanced gastric cancer is the third leading cause of cancer-related death worldwide (1). In the early stages, gastric cancer can often be cured by complete surgical resection with lymphadenectomy, whereas patients with advanced cancer have a poor prognosis. Although the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer, a randomized phase III trial in patients with stage II/III gastric cancer revealed a prolonged 5-year survival rate of 50-84% (2), the prognosis of patients with metastatic and recurrent cancer remains poor with a median overall survival of approximately 1 year (3,4). Variety different metastatic patterns, such as hematogenous, lymphogenic, and disseminated metastasis, prevent proper treatment and result in a poor prognosis. Identifying a more effective and easy-to-use clinical marker may lead to more effective multidisciplinary treatments and more optimal postoperative surveillance.

Cancer progression produces many systemic biological reactions including metabolic disorders, neuroendocrine responses, and cytokine expression (5-7). Angiogenesis plays a fundamental role in tumor growth, malignant transformation, and invasion of tumor cells (8,9), and overexpression of proangiogenic cytokines, such as vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), platelet-derived endothelial cell growth factor, and hepatocyte growth factor (HGF), is correlated with increased cancer infiltration and poor prognosis in patients with gastric cancer (10-14). VEGF is a key regulator of tumor-associated angiogenesis. Recent reports have demonstrated that the circulating serum level of VEGF is correlated with recurrence and survival in patients with gastric cancer and is thus, a useful biomarker for postoperative follow-up and monitoring patients' responses to chemotherapy (15-18). Systemic changes in tissue circulation may be expected secondary to circulating proangiogenic cytokines; however, the relationship between tissue hemodynamic changes and cancer progression has not been reported.

Perfusion computed tomography (PCT) is a less invasive imaging modality that provides information about tissue hemodynamics at the capillary level in quantitative procedures. Since PCT was first performed in a patient with stroke (19), it has been applied clinically in a variety of liver conditions (20-22), and recent reports have discussed its clinical utility for cancer characterization, predicting the response to chemoradiotherapy, assessing the response to these therapies, and predicting patient outcomes (23-25).

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In this study, we hypothesized that cancer-associated systemic changes secondary to biological reactions and circulating cytokines might affect and alter tissue circulation. Therefore, we investigated hepatic blood flow (HBF) as a surrogate marker because the liver, as an abundant blood-supplied organ, may amplify changes in systemic tissue perfusion, and may be an appropriate and easy target organ to assess by CT.

Materials and methods

Patient population. This study was approved by the institutional review board (IRB) of the Medical Ethical Committee of Teikyo University (Ichihara, Japan), and written informed consent was obtained from all patients (IRB number, 12-179; UMIN000019970). We enrolled 166 consecutive patients with histologically-proven gastric adenocarcinoma who were treated at Teikyo University Chiba Medical Center, Ichihara, Japan from March 2013 to December 2017. The eligibility criteria were as follows: (i) age ≥20 years; (ii) no liver dysfunction, cirrhosis, or jaundice (serum alanine aminotransferase level <120 IU/l, serum total bilirubin level <2.0 mg/dl, and blood platelet count >150,000/μl); (iii) adequate renal function (serum creatinine level <2.0 mg/dl); (iv) absence of multiple liver metastases (≤3 cm in diameter and ≤3 lesions); (v) no inflammation (C-reactive protein level <3.0 mg/dl and white blood cell count <12,000/μl); and (vi) no other history of active malignant neoplasms. We excluded 30 patients whose acquired images were not suitable for analysis because of an insufficient concentration of the contrast agent or excessive respiratory movements (n=18) or who refused medical intervention (n=12). Finally, we included 136 patients; 15 (11%) patients had synchronous liver metastasis, and the median follow-up duration was 685 days (range, 17-1923 days) (Table I).

Cancer staging and treatment. The location and size of the tumors were clinically determined by gastrointestinal endoscopy and biopsy specimens, contrast-enhanced CT, magnetic resonance imaging, and barium contrast radiography. The tumor-node-metastasis (TNM) classification of the Union for International Cancer Control (26) was used for evaluation. In total, 103 patients underwent surgical resection; the remaining 33 had inoperable disease. In the operable group, 24 received two or three cycles of neoadjuvant chemotherapy using CS (S-1 with cisplatin) or SOX (S-1 with oxaliplatin). Gastrectomy with D0 or D1 lymph node dissection, including palliative resection, was performed for clinical T1a, N0 cancer and stage IV disease, otherwise we performed gastrectomy with D1+ or D2 dissection. The extent of lymph node dissection was determined according to the Japanese Classification of Gastric Carcinoma (27). Patients with pathological stage II/III disease received postoperative adjuvant chemotherapy with S-1 for 1 year. In the inoperable group, CS or SOX were administered as first-line chemotherapy, and ramucirumab and paclitaxel as second-line therapies, if possible (Table I).

Liver PCT imaging protocol. Liver PCT was performed with a 64-row multidetector CT scanner (LightSpeed VCT; GE Medical Systems, Milwaukee, WI, USA). After checking patients' vital signs, we administered supplemental oxygen at 3 l/min for 10 min through a venturi mask in the supine position on the scanner table. A non-enhanced CT scan was obtained for initial liver localization. Eight sequential 5-mm-slice scans with a total length of 4-cm thickness of the liver, including the hepatic hilum, were selected. Contrast material (370 mg iodine/ml, Iopamiron 370; Bayer Healthcare, Leverkusen, Germany) was administered to a total dose of 0.8 ml/kg at a rate of 5 ml/s with a 20-ml saline chaser using a power injector (Dual Shot GX; Nemoto Kyorindo, Tokyo, Japan). A dynamic study of the selected slices was then performed during a breath hold at a static table position. Images were obtained with the following parameters: 10-sec start delay, 40-mm beam collimation, 120-kV tube voltage, 60-mA tube current, 1-sec gantry rotation time, and 1-sec inter-scan delay. PCT was performed before initial treatment in all patients and at 6-month intervals postoperatively in patients who underwent gastrectomy.

Imaging interpretation. Image data were transferred to an image-processing workstation (Advantage Workstation ver. 4.4; GE Medical Systems) and analyzed by the commercially-based CT perfusion software of a noncompartment model with a dual-input deconvolution method (CT Perfusion ver. 4; GE Medical Systems). Analyses were based on the following principles: Contrast material injected as a rapid bolus fills the entire capillary network, arrives at equilibrium, and then washes out from the tissue network. Because iodinated contrast material can be considered a purely intravascular tracer on dynamic CT, its concentration within tissue can be obtained by the arterial and portal input; change in contrast material volume is shown as the impulse retention function (28). Input perfusion data were determined by placing a region of interest in the abdominal aorta (median area, 121 mm^2; range, 22-328 mm^2) and in the portal vein trunk (median area, 33 mm^2; range, 10-99 mm^2). Time-density curves of the abdominal aorta and the portal vein were automatically generated for blood input, and the data were processed into a functional map representing HBF (ml/min/100 g tissue).

HBF was calculated in the workstation, and a functional map was displayed in colors ranging from blue to red with red being the higher range. A freehand region of interest in the liver was traced on enhanced gray-scale raw CT images according to the following rules: A line was drawn around the entire right hepatic lobe, including the medial segment, if possible; a 1-2-cm margin from the hepatic surface was ensured; and intrahepatic lesions, if present, were excluded (e.g., cyst, hemangioma, and metastatic lesions). HBF values in the four central slices, which were selected to include the maximum hepatic plane, were then averaged and used for evaluation (Fig. 1).

Analysis of serum proangiogenic factors. Serum proangiogenic cytokines were investigated in the last 40 patients who participated in an additional research project under IRB approval and with written informed consent (IRB number, 15-007; UMIN000019973). Peripheral blood samples were collected and centrifuged to separate the serum, which was then stored at -80˚C. Electrochemiluminescence immunoassays were used for detection. Serum samples were tested in

Table I. Characteristics of patients with gastric cancer.

Total characteristics	Total (n=136)
Age (years)	72 (40-90)
Sex	
Male	110
Female	26
Tumor location	
Upper	32
Middle	48
Lower	56
Histological type	
Intestinal	60
Diffuse	76
Tumor size (mm)	55 (7-180)
Clinical stage	
I	42
II	20
III	32
IV	42
Operable patients	103
Neoadjuvant chemotherapy	
Yes	24
No	79
Extent of gastrectomy	
Distal-proximal gastrectomy	75
Total gastrectomy	28
Pathological stage	
I	43
II	21
III	25
IV	14
Inoperable patients	33
Main cause of inoperability	
Dissemination	15
Distant metastasis	14
Infiltration into adjacent organs	4
Treatment	
Chemotherapy only	23
Chemotherapy + bypass operation	10

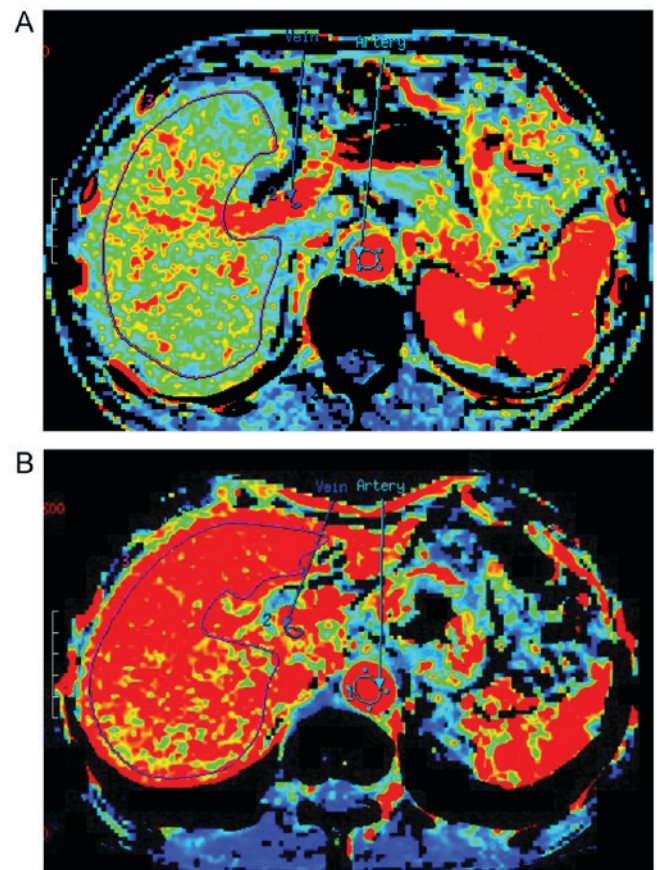Continuous values are expressed as median (range).

Figure 1. Hepatic blood flow (HBF) maps of liver perfusion CT. (A) A patient with stage I cancer (T1, N0) with preoperative HBF of 158 ml/min/100 g tissue. (B) A patient with stage IV cancer who underwent laparotomy that revealed unresectable cancer secondary to dissemination, with preoperative HBF of 310 ml/min/100 g tissue.

duplicate for concentrations of VEGF, VEGF receptor-2 (VEGFR-2), HGF, and angiopoietin-1 under standard conditions. The following enzyme-linked immunosorbent assays (ELISA) (DuoSet™ ELISA; R&D Systems, Minneapolis, MN, USA) were performed to quantify serum levels using standard curves for concentration calculation according to the manufacturer's protocols: DuoSet ELISA Human VEGF (DY293B), DuoSet ELISA Human VEGFR2/KDR (DY357), DuoSet ELISA Human HGF (DY294), and DuoSet ELISA Human Angiopoietin-1 (DY923). ELISA readings were measured at 450 nm in a microplate reader (ARVO X multilabel reader; PerkinElmer, Waltham, MA, USA).

Statistical analysis. Statistical significance was evaluated by the Mann-Whitney U test for comparison of two continuous parameters and the Chi-square test for categorical variables. One-way analysis of variance was used to analyze the differences among three or more groups performing the Dunnett's test. The correlations between two continuous values were plotted by a linear regression model and evaluated by Pearson's correlation test. A Cox proportional hazard regression model was used to analyze prognostic factors in univariate and multivariate analyses. A multiple logistic regression was calculated to predict HBF based on significant clinical factors with univariate analyses. Overall survival curves were plotted by the Kaplan-Meier method, and the differences were statistically evaluated by the log-rank test. Two-tailed P-values <0.05 were considered significant. All statistical analyses were performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA).

Results

HBF and clinicopathological factors. The median HBF was 217 ml/min/100 g tissue (range, 128-430 ml/min/100 g tissue).

Table II. Comparison between hepatic blood flow and clinicopathological factors.

Variables	Category of HBF		P-value
	Low (n=67)	High (n=69)	
Age (years)	73 (51-89)	69 (40-90)	0.230
Gender, n (%)			0.097
Male	58 (87)	52 (75)	
Female	9 (13)	17 (25)	
BMI (kg/mm^2)	22.7 (16.0-34.2)	20.1 (12.9-27.4)	<0.001
Hb (g/dl)	13.9 (7.6-17.1)	11.3 (7.3-15.2)	<0.001
AST (IU/l)	21 (12-70)	20 (12-85)	0.440
ALT (IU/l)	18 (7-88)	15 (5-68)	0.081
Cre (mg/dl)	0.81 (0.40-1.52)	0.77 (0.26-1.40)	0.143
SBP (mmHg)	123 (93-160)	116 (90-158)	0.146
Heart rate (bpm)	74 (48-103)	76 (58-111)	0.299
Ejection fraction (%)	64.8 (40.0-78.4)	63.7 (33.2-83.1)	0.442
Valvular heart disease, n (%)			0.295
Yes	23 (34)	18 (26)	
No	44 (66)	51 (74)	
Tumor location, n (%)			0.471
Upper	14 (21)	18 (26)	
Middle	27 (40)	21 (30)	
Lower	26 (39)	30 (44)	
Histological type, n (%)			0.004
Intestinal	38 (57)	22 (32)	
Diffuse	29 (43)	47 (68)	
Tumor size (mm)	43 (7-110)	71 (13-180)	<0.001
Depth of invasion[a], n (%)			<0.001
T1/T2	41 (61)	8 (12)	
T3/T4	26 (39)	61 (88)	
Lymph node metastasis[a], n (%)			<0.001
N0/N1	49 (73)	23 (33)	
N2/N3	18 (27)	46 (67)	
Distant metastasis[a], n (%)			<0.001
M0	63 (94)	38 (55)	
M1	4 (6)	31 (45)	

Continuous values are expressed as median (range). HBF, hepatic blood flow; High BF, greater than or equal to the median; BMI, body mass index; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cre, creatinine; SBP, systolic blood pressure. Low HBF, less than the median (<217 ml/min/100 g tissue). [a]Include both pathological findings in operable patients and clinical findings in inoperable patients.

When patients were divided by the median value, the two groups differed significantly in body mass index (BMI), and blood hemoglobin (Hb) level, whereas results were similar for liver, renal, and cardiac functional data. The high-HBF group contained more diffuse-type cancer (43% vs. 68%, P=0.004), larger tumors, (43 mm vs. 71, P<0.001), and more advanced tumor-node stages (Table II). Mean HBFs by clinical disease stage were stage I: 183 ml/min/100 g tissue (range, 133-323 ml/min/100 g tissue); stage II: 191 ml/min/100 g tissue (range, 128-296 ml/min/100 g tissue); stage III: 241 ml/min/100 g tissue (range, 169-320 ml/min/100 g

tissue); and stage IV: 263 ml/min/100 g tissue (range, 176-430 ml/min/100 g tissue). Patients with stage III/IV disease had significantly higher HBF than did those with stage I/II disease. We saw no difference between patients with stage I and II cancer (P=0.959) vs. those with stage III and IV cancer (P=0.088) (Fig. 2).

Postoperative change in HBF. Fourteen patients were excluded because of renal dysfunction by chemotherapy (n=8), iodic allergic reaction (n=4), and death within 6 months (n=2) during postoperative follow-up. Comparing preoperative
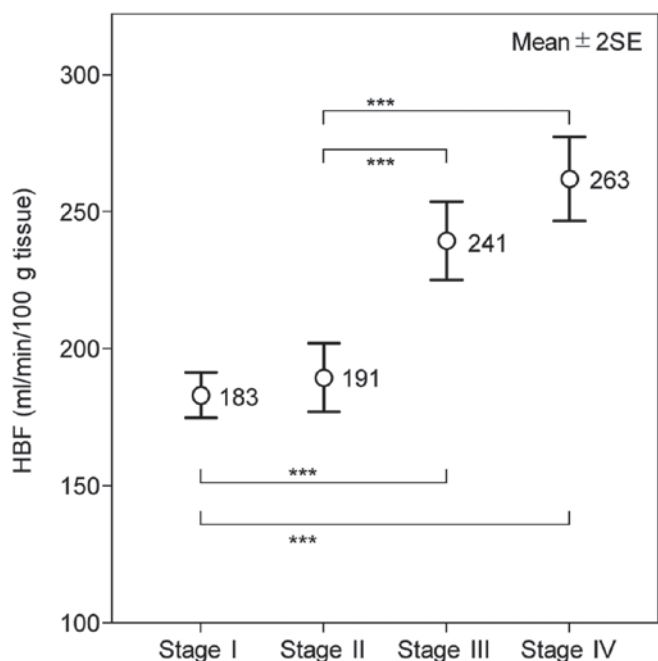
Figure 2. HBF at each clinical stage. ***P<0.001. HBF, hepatic blood flow; Stage, clinical stage; numerical number, mean value; SE, standard error.

HBF and results 6 months postoperatively, both were statistically similar in patients with pathological stage I/II disease (n=56, 183 ml/min/100 g tissue vs. 188 ml/min/100 g tissue, P=0.833). Meanwhile postoperative HBF deceased significantly in patients with pathological stage III/IV disease (n=33, 232 ml/min/100 g tissue vs. 207 ml/min/100 g tissue, P=0.002) (Fig. 3).

HBF and prognosis. Median HBF for operable vs. inoperable patients was 201 ml/min/100 g tissue (range, 128-430 ml/min/100 g tissue) vs. 258 ml/min/100 g tissue (range, 188-394 ml/min/100 g tissue). When both patient groups were compared by their respective median HBF values, the high-HBF group had a significantly worse prognosis (P=0.002 and P=0.024), notably in the inoperable group, with <1-year survival (Fig. 4).

Postoperative HBF in patients with recurrent gastric cancer. The median postoperative follow-up duration was 740 days (range, 43-1923 days). Seventeen (17%) patients had recurrent disease and a median HBF preoperative, 6 months' postoperatively, and recurrent of 212 ml/min/100 g tissue (range, 128-430 ml/min/100 g tissue), 191 ml/min/100 g tissue (range, 141-375 ml/min/100 g tissue), and 246 ml/min/100 g tissue (range, 171-374 ml/min/100 g tissue), respectively. HBF at disease recurrence was significantly higher compared with HBF 6 months postoperatively (P=0.002) and preoperatively (P=0.015). Two patients underwent repeat surgery. When recurrent patients were divided by the median HBF value at recurrence, the high-HBF group had a significantly worse postrecurrent prognosis (P=0.019) (Fig. 5).

Prognostic significance of HBF. Clinical parameters assessed in Table II were evaluated by univariate analyses in all patients, then variables with significant difference were entered into the multivariate analysis. On behalf of cancer status, tumor depth and node metastasis were applied for analysis. As a result, HBF was an independent prognostic factor [hazard ratio (HR), 2.019; P=0.048] as were node
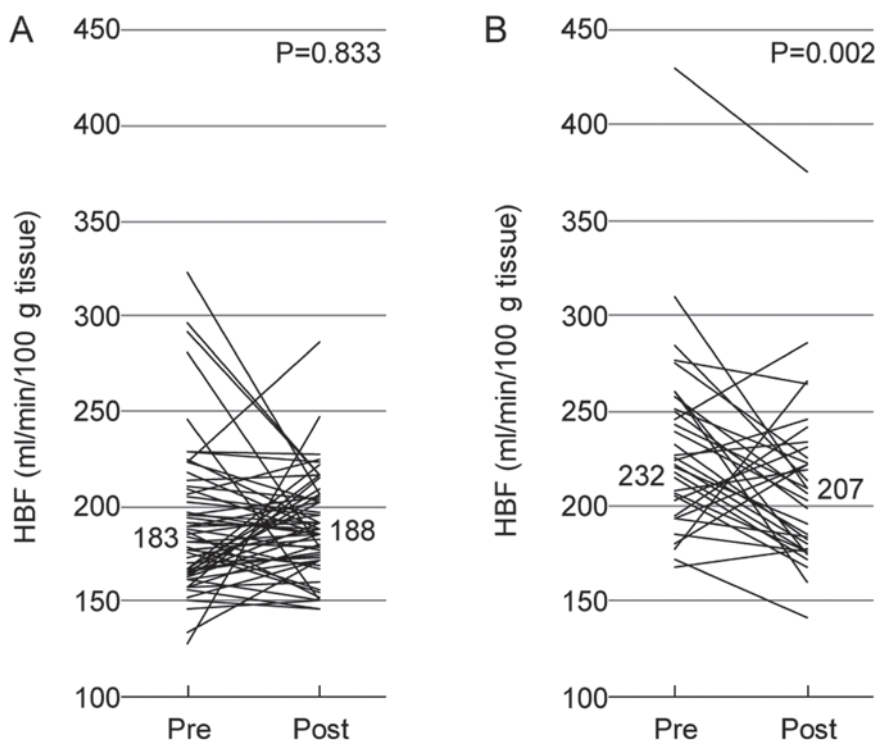

Figure 3. Postoperative change in HBF. HBF, hepatic blood flow; pre, preoperative; post, 6 months postoperatively; bold numerical number, median value. (A) Patients with pathological stage I/II disease (n=56), (B) Patients with pathological stage III/IV disease (n=33).
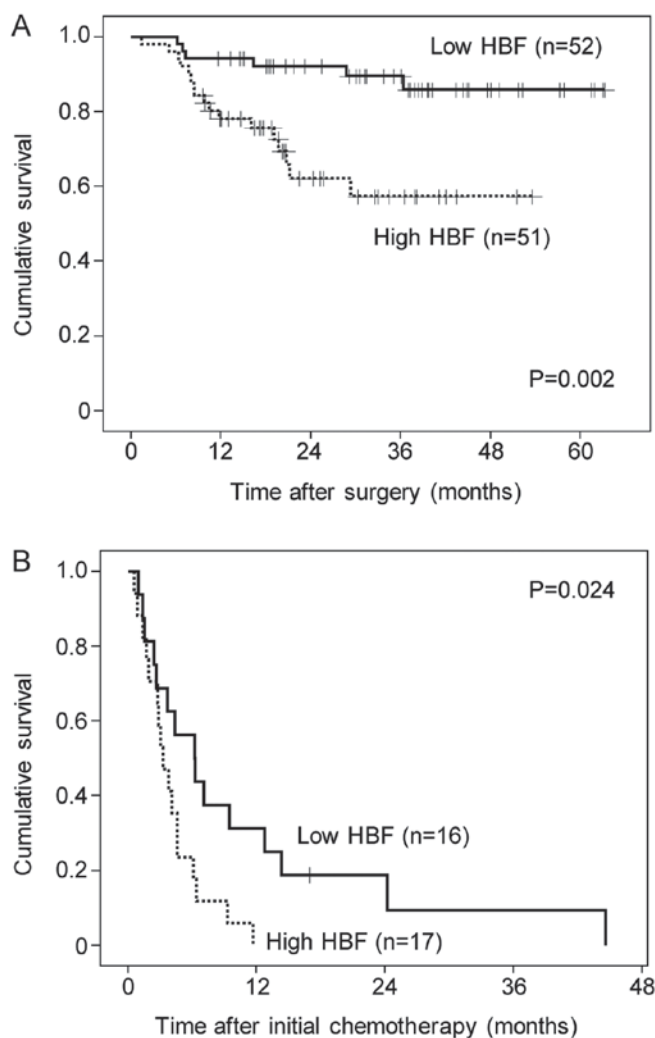
Figure 4. Overall survival curves of (A) operable and (B) inoperable patients. HBF, hepatic blood flow; Low HBF (solid line), less than the median HBF; High HBF (dashed line), greater than or equal to the median HBF.
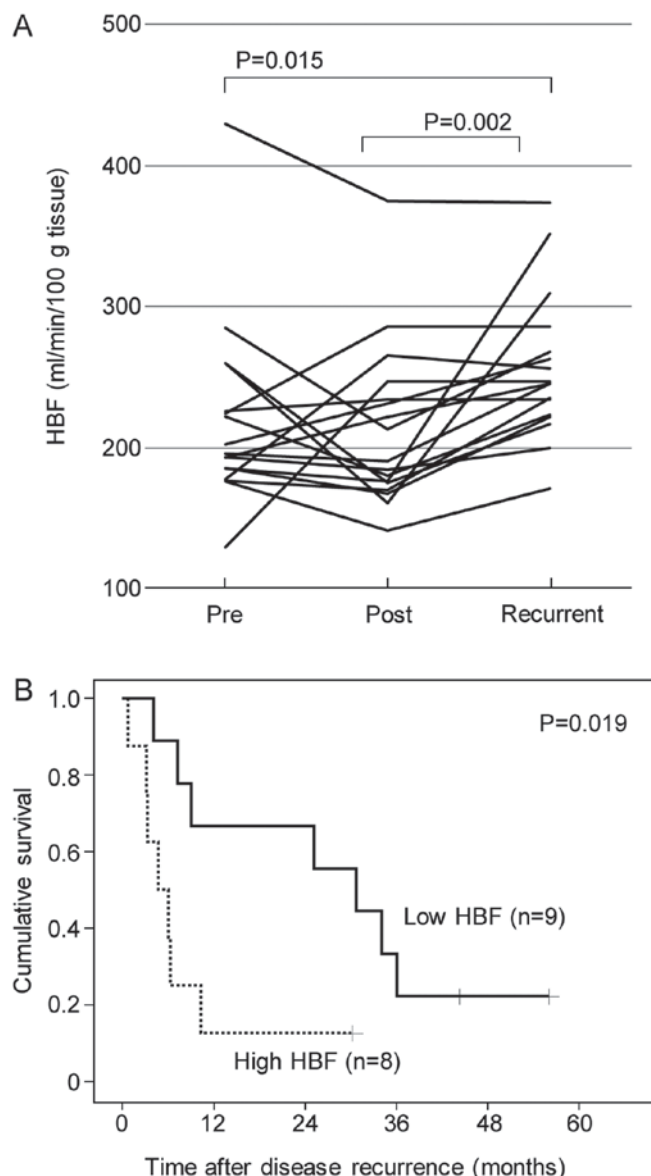

Figure 5. Postoperative HBF change and postrecurrent survival in patients with recurrent gastric cancer. (A) HBF at disease recurrence was significantly higher compared with HBF 6 months postoperatively (246 ml/min/100 g tissue vs. 191, P=0.002) and preoperatively (246 ml/min/100 g tissue vs. 212, P=0.015). (B) When recurrent patients were divided according to the median HBF value at recurrence (246 ml/min/100 g tissue), the high-HBF group had a significantly worse postrecurrent prognosis (P=0.019). HBF, hepatic blood flow.

metastasis (HR, 3.339; P=0.002) and histological type (HR, 2.259; P=0.014) (Table III).

HBF and serum proangiogenic cytokines. HBF was strongly correlated with VEGF (R=0.607, P<0.001) and weakly correlated with HGF (R=0.277, P=0.083). No correlation was observed between HBF and either VEGFR-2 or angiopoietin-1 (Fig. 6).

Predictive factors for HBF. Clinical parameters assessed in Table II were evaluated by univariate analyses, then variables with significant difference were entered into the multifactorial analysis. As a result, BMI [odds ratio (OR), 4.754; P=0.001] and Hb (OR, 2.576; P=0.040) were independent predictive factors for HBF as was tumor depth (OR, 4.351; P=0.028) (Table IV).

Discussion

Previous applications of PCT for gastrointestinal cancer. Previous reports discussed the relationship between tumor blood flow assessed by PCT and malignant behaviors in tumors.

Hayano *et al* demonstrated that tumors with low blood flow tended to be accompanied by synchronous metastatic lymph nodes or distant metastases and associated with poor patient survival in colorectal cancer (29). They concluded that tumor growth might lead to increase both tissue pressure and capillary compression and subsequently reduce tumor blood flow, as a result, hypoxic environment in tumor tissue might promote oncogenic mutations and finally more aggressive behaviors in tumor. Another paper reported that neoadjuvant therapy was more effective in patients with higher baseline tumor blood flow and patients with a positive treatment response showed decrease tumor blood flow in gastric cancer (30). Previous reports applied PCT for assessing tumor neovascularization and focused on predicting patient prognosis and response to

Table III. Prognostic parameters by univariate and multivariate analysis.

Variables	Category	n	Univariate analysis			Multivariate analysis		
			HR	95% CI	P-value	HR	95% CI	P-value
BMI (kg/mm²)	<21.5	68	1.883	1.092-3.249	0.023	1.108	0.605-2.031	0.739
	≥21.5	68	Reference					
Hb (g/dl)	<12.6	68	2.877	1.629-5.080	<0.001	1.361	0.754-2.458	0.306
	≥12.6	68	Reference					
Histological type	Diffuse	76	3.684	1.970-6.890	<0.001	2.259	1.183-4.314	0.014
	Intestinal	60	Reference					
Tumor depth[a]	T3/T4	87	9.089	3.589-23.017	<0.001	2.184	0.709-6.733	0.174
	T1/T2	49	Reference					
Node metastasis[a]	N2/N3	64	7.416	3.806-14.449	<0.001	3.339	1.587-7.281	0.002
	N0/N1	72	Reference					
HBF	≥217	69	4.192	2.295-7.657	<0.001	2.019	1.006-4.051	0.048
(ml/min/100 g tissue)	<217	67	Reference					

Continuous values are categorized by the median value. HR, hazard ratio; CI, confidence interval; BMI, body mass index; Hb, hemoglobin; HBF, hepatic blood flow. [a]Include both pathological findings in operable patients and clinical findings in inoperable patients.
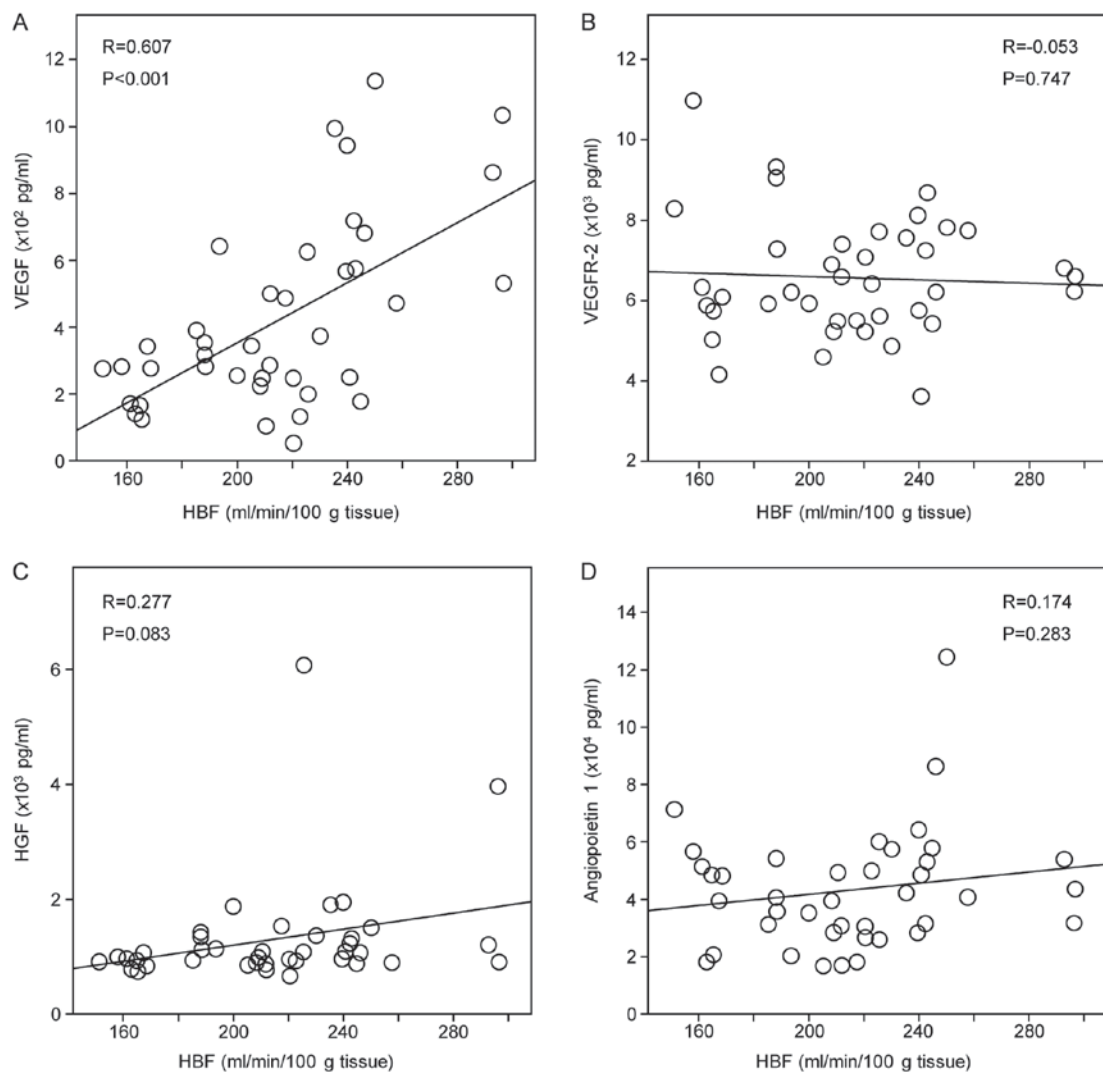

Figure 6. Correlation between HBF and serum proangiogenic cytokines. (A) HBF vs. VEGF, (B) HBF vs. VEGFR-2, (C) HBF vs. HGF, and (D) HBF vs. angiopoietin-1. HBF, hepatic blood flow; VEGF, vascular endothelial growth factor; VEGFR-2, VEGF receptor-2; HGF, hepatocyte growth factor.

Table IV. Predictive factors for high hepatic blood flow by logistic regression analysis.

Variables	Category	Regression coefficient	Odds ratio	95% CI	P-value
Sex	Female	0.224	1.251	0.396-3.949	0.703
BMI (kg/mm^2)	<21.5	1.520	4.754	1.815-11.523	0.001
Hb (g/dl)	<12.6	0.946	2.576	1.042-6.370	0.040
Tumor size (mm)	≥55	0.148	1.159	0.398-3.373	0.787
Histological type	Diffuse	0.240	1.271	0.505-3.198	0.661
Tumor depth[a]	T3/T4	1.470	4.351	1.172-16.153	0.028
Node metastasis[a]	N2/N3	0.747	2.111	0.736-6.050	0.164

High hepatic blood flow, greater than or equal to the median (≥217 ml/min/100 g tissue). Continuous values are categorized by the median value. CI, confidence interval; BMI, body mass index; Hb, hemoglobin. [a]Include both pathological findings in operable patients and clinical findings in inoperable patients.

chemotherapy or chemoradiotherapy (23-25). The application of present study is quite different from these previous reports. We assessed hepatic perfusion as a surrogate marker of tissue hemodynamic changes that might arise in the process of cancer progression.

HBF in patients with gastric cancer. Although previous reports demonstrated increased HBF in patients with synchronous liver metastasis with digestive cancer using scintigraphy and Doppler ultrasonography more than two decades ago (31,32), HBF was not further discussed because of quantitative difficulties in its measurement. Since hepatic PCT was introduced into clinical practice, it has been recognized as a valid clinical method for early detection of obscure liver micrometastasis with incremental arterial flow by intrahepatic neovascularization (33-36). However, our concept differs from these studies because we evaluated cancer-associated systemic change using hepatic perfusion.

In this study, we demonstrated a relationship between HBF and gastric cancer progression. HBF increased in association with larger tumor size, increased depth of tumor invasion, lymph node metastasis, and stage. Postoperatively, HBF declined in resectable gastric cancer patients with advanced stage III/IV disease, and increased further in recurrent cases. The high-HBF group had a significantly worse prognosis in all patient groups: Operable, inoperable, and recurrent disease. Moreover, HBF was an independent prognostic imaging biomarker for gastric cancer in multivariate analysis, in our study. HBF might reflect the systemic change in tissue circulation developed by cancer progression. Patients with stage I cancer and with stage II had the same HBF; conversely, patients with stage III/IV cancer had significantly increased HBF levels. We presume that stage III disease may be systemic and require systemic therapies as well as locoregional treatment. This affirms the necessity of pre- and postoperative systemic chemotherapy for patients with stage III gastric cancer, currently a popular topic in gastric cancer treatment (37-39). To our knowledge, few studies have discussed cancer progression focusing on HBF (40).

Mechanism of increased HBF. Although we could not clarify the reason for the HBF increase in this study, we speculate two indirect mechanisms under cancer progression. The first is changes in a patient's general condition, and the second is the impact of circulating proangiogenic factors. The high-HBF group in our study had significantly lower BMI and lower Hb levels. BMI and Hb were also independent predictive factors for HBF by multifactorial analysis as were tumor depth. These results suggest that HBF may be influenced by BMI and Hb level as well as cancer status. We deem at the current moment that HBF may indirectly increase with lower abdominal pressure secondary to visceral fat loss and also may increase secondary to the intrahepatic vascular response to maintain hepatic perfusion with anemia. HBF might be a reflection of these changes in physical status associated with cancer progression.

Platelets isolated from cancer patients contain more VEGF than those from healthy controls (41,42). Localized platelet aggregation may contribute to tumor progression by releasing a variety of vasoactive and proangiogenic substances in the tumor and may contribute to metastasis by facilitating adherence of disseminated tumor cells to capillary walls at distant sites (43,44). We consider that these circulating vasoactive and proangiogenic substances in patients with advanced disease may affect hepatic perfusion. VEGF and, comparatively, HGF likely play roles in these vasoactive responses.

Clinical relevance of HBF. The clinical utility of serum tumor markers remains controversial. Although many tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), have been studied in the monitoring of gastric cancer, none has sufficient sensitivity. The respective sensitivities of CEA and CA 19-9 for predicting gastric cancer recurrence are 31-66 and 16-55%, which seems rather low (45). Postoperative HBF monitoring might predict cancer recurrence, and even in recurrent disease, aggressive or supportive treatment might be selected based on HBF in the future; however, further investigations are needed in this respect.

Limitations. Since HBF is evaluated by dynamic CT imaging during a nearly 1-min breath hold, excessive respiratory movement prevents accurate analysis. Moreover, we were not able to clarify the normal range for HBF in this preliminary study.

Further study is warranted to identify the relationship between HBF and cancer progression and recurrence including hepatic histological evaluations in larger samples.

In conclusion, HBF increases in association with gastric cancer progression. Patients with advanced gastric cancer and recurrent disease had significantly increased HBF. HBF may be an easily assessed and independent imaging biomarker for predicting patient survival.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KS, TF and AS concepted and designed of study. MM, CK and KN acquired imaging data. KS, KH and SN analyzed and interpreted the patient data. MM performed the histological evaluation. HS and KK contributed in acquiring clinicopathological data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the institutional review board (IRB) of the Medical Ethical Committee of Teikyo University (Ichihara, Japan), and written informed consent was obtained from all patients (IRB number, 12-179; UMIN000019970 and IRB number, 15-007; UMIN000019973).

Patient consent for publication

Written informed consent was obtained from the patient for publication of this research.

Competing interests

The authors declare that they have no competing interests.

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