Advanced Hepatocellular Carcinoma: CT Perfusion of Liver and Tumor Tissue—Initial Experience[1]

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Purpose: To prospectively assess computed tomographic (CT) perfusion for evaluation of tumor vascularity of advanced hepatocellular carcinoma (HCC) and to correlate CT perfusion parameters with tumor grade and serum markers.

Materials and Methods: The study was HIPAA compliant and was approved by the institutional review board. Patients provided informed consent. Thirty patients (22 men, eight women; mean age, 60 years; range, 28–79 years) with unresectable or metastatic HCC were studied. Dynamic first-pass CT perfusion was performed in primary ($n = 25$) and metastatic ($n = 5$) HCCs after intravenous injection of contrast medium. Data were analyzed to calculate tissue blood flow, blood volume, mean transit time, and permeability–surface area product. Repeat examination was performed in four patients within 30 hours to test reproducibility of CT perfusion. CT perfusion parameters were compared among tumors of different grades, with presence or absence of portal vein invasion, with presence or absence of cirrhosis, and of various extrahepatic metastases. Parameters were correlated with HCC serum markers. One-way analysis of variance was used to calculate variations in CT perfusion parameters.

Results: Good correlation ($r = 0.9$, $P < .01$) was observed between repeat examination results and first CT examination results. There was a significant difference ($P \leq .05$) in CT perfusion parameters between primary HCC and background liver parenchyma. Well-differentiated HCC showed significantly higher perfusion values ($P \leq .05$) than other grades. There was no significant difference in tumor perfusion between presence or absence of portal vein invasion or cirrhosis. Lymph node metastasis demonstrated lower values compared with metastases from other extrahepatic sites. There was no significant correlation between CT perfusion parameters and serum markers.

Conclusion: Results suggest that CT perfusion is a feasible and, from the limited data, reproducible technique for quantifying tumor vascularity and angiogenesis in advanced HCC.

Supplemental material:
http://radiology.rsnajnls.org/cgi/content/full/243/3/736/DC1

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Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and is responsible for more than 500 000 deaths every year globally (1). In the United States, it most often occurs in patients with preexisting cirrhosis or chronic hepatitis. HCCs are highly vascular and derive neovasculature through the process of angiogenesis (2,3). Tumor angiogenesis is a complex process mediated by several angiogenic and antiangiogenic factors and is critical for tumor growth and metastasis (4). Therefore, quantifying tumor angiogenesis is important for risk stratification, evaluation of disease progression, and monitoring response to therapy (5,6). Currently, tissue sampling for the evaluation of tumor microvessel density is considered the most accurate direct marker of angiogenesis. However, tissue sampling is invasive and therefore impractical for longitudinal patient monitoring (7). Consequently, an accurate noninvasive method to quantify tumor angiogenesis would be highly desirable.

Computer tomographic (CT) perfusion is a technology that allows quantitative assessment of various parameters, such as tumor blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability–surface area product (PS). Reports of many studies (8–11) have described the use of CT perfusion for tumors in the brain, as well as its utility for tumors in the liver, lung, pancreas, and head and neck.

The purpose of our study was to prospectively assess CT perfusion for evaluation of tumor vascularity of advanced HCC and to correlate CT perfusion parameters with tumor grade and serum markers.

Advances in Knowledge

- The perfusion parameters of well-differentiated hepatocellular carcinoma (HCC) were found to be distinct from those of moderately and poorly differentiated HCC.
- The presence of cirrhosis or angioinvasion does not result in significant alteration in tumor perfusion.
- No correlation between CT perfusion parameters and serum α-fetoprotein levels could be established.

Materials and Methods

Study Design

This study was part of a phase II clinical study on advanced HCC (12). This study was in compliance with Health Insurance Portability and Accountability Act regulations and was approved by the institutional review board. All patients were required to provide written informed consent before study participation according to institutional and federal guidelines. Inclusion and exclusion criteria were as detailed before (12) and included the following relevant parameters for the CT perfusion study: *(a)* patients had histopathologically proved measurable locally advanced, recurrent, or metastatic HCC; *(b)* they had adequate renal function (serum creatinine level ≤ 2.0 mg/dL [177 μmol/L]); and *(c)* the diameter of the tumor was more than 2 cm. Between July 2004 and January 2005, 30 of 33 enrolled subjects met our criteria and agreed to participate in this study.

Study Cohort

The study cohort included 22 men and eight women (age range, 28–79 years; mean age, 60 years) with a biopsy-confirmed diagnosis of HCC. We divided our cohort into two groups. Patients undergoing CT perfusion at the site of primary HCC, with or without portal vein invasion or with or without cirrhosis, were included in group A (n = 25) (17 men, eight women; mean age, 61 years; age range, 48–79 years). Patients undergoing CT perfusion for extrahepatic metastases or for follow-up after resection of the primary tumor were included in group B (n = 5) (five men; mean age, 53 years; age range, 28–74 years). The TNM staging in the study population at manifestation on the basis of CT results alone (n = 14) or on the basis of both CT and magnetic resonance imaging results (n = 16) was as follows: T3N0M0 (n = 15), T3N1M0 (n = 1), T4N0M0 (n = 7), and T4N1M0 (n = 2) in group A; and N0M1 (n = 2) and N1M1 (n = 3) in group B.

CT Perfusion Technique

CT perfusion was performed with a 16-section multidetector CT scanner (LightSpeed; GE Medical Systems, Milwaukee, Wis). For initial localization of the tumor, a CT scan of the abdomen (or chest or pelvis for group B) was obtained without contrast medium during a breath hold at the end of expiration. After tumor localization, a 2-cm tumor region was selected independently by an author (D.V.S., with 11 years of experience in interpretation of abdominal CT) for the dynamic study in the maximal diameter of the tumor. A dynamic study of the selected area was performed in a single breath hold at the end of expiration at a static table position. A total of 70 mL of nonionic iodinated contrast medium (Isovue; Bracco, Princeton, NJ) (300 mg of iodine per milliliter) was injected at a rate of 7 mL/sec through an 18-gauge intravenous cannula. The following CT parameters were used to acquire dynamic data: 1-second gantry rotation time, 100 kVp, 240 mA, acquisition in 4i transverse mode (four sections per gantry rotation), and 5-mm reconstructed section thickness. Scanning was initi-

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Abbreviations:
BF = blood flow
BV = blood volume
HCC = hepatocellular carcinoma
MTT = mean transit time
PS = permeability–surface area product
ROI = region of interest

Author contributions:
Guarantors of integrity of entire study, D.V.S., N.S.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, D.V.S., N.S.H.; clinical studies, all authors; statistical analysis, D.V.S., N.S.H.; and manuscript editing, D.V.S., N.S.H., P.R.M.

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ated after a 5-second delay from the start of injection, and images were acquired for a total duration of 25 or 30 seconds. We chose a duration of either 25 or 30 seconds for dynamic scanning on the basis of patient maximum breath-hold capacity to limit radiation dose and to avoid respiratory artifacts from longer breath holds. To test the reproducibility of CT perfusion, the examination was repeated in four patients (in group A) by using the same technique after 24 hours (range, 24–30 hours) and before initiation of any therapy.

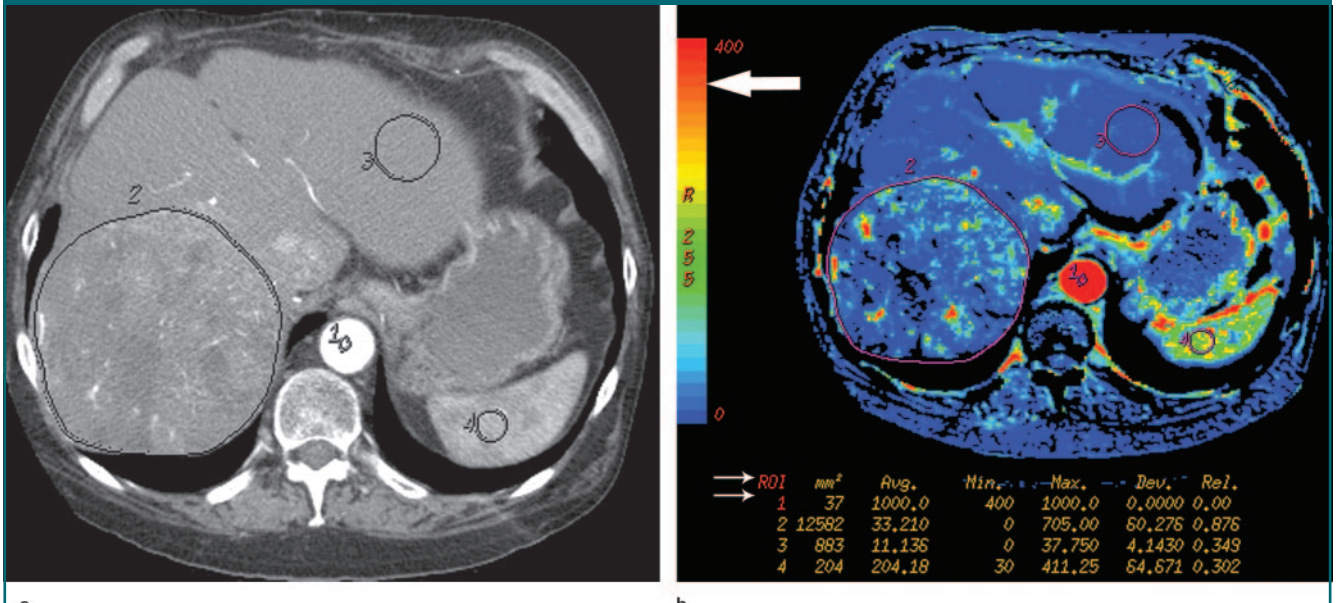
Data Analysis

Data were processed at a workstation (Advantage Windows 4.0; GE Medical Systems) with CT perfusion software (GE Perfusion 2.0) by a radiologist (N.S.H.) with 5 years of experience in radiology and 1 year of experience in gastrointestinal radiology and CT perfusion software. Definitions of CT perfusion parameters and the model used for generating maps are described in Appendix E1 *(http://radiology.rsnajnls.org/cgi/content/full/243/3/736/DC1)*. Functional maps of BF, BV, MTT, and PS were generated. Functional maps were obtained by *(a)* displaying images at an appropriate window, such as soft tissue for abdomen (width = 400 HU, level = 40 HU); *(b)* selecting sections between the beginning and end of contrast enhancement in the aorta either automatically or manually; and *(c)* obtaining a reference arterial input curve by placing a region of interest (ROI) in the aorta (range, 12–28 mm^2) manually (except in one patient with pelvic bone metastases, in whom the ROI was placed in the external iliac artery). We ensured that the ROI placed in the aorta (or the external iliac artery) did not include any mural calcification.

ROIs for tumors (range, 125–117 977 mm^2) were hand drawn in all four anatomic section locations obtained in each patient. In the presence of multiple tumors, ROIs were drawn for all tumors more than 20 mm in size, and a mean value from all the lesions was used for analysis. To draw ROIs, we selected sections in which the tumor demonstrated maximal enhancement to avoid adjacent normal vasculature. Similarly, ROIs were drawn in background liver parenchyma (range, 140–1550 mm^2) and spleen (range, 110–525 mm^2) in the same four sections (Fig 1a) in patients with a primary tumor. ROIs of the background liver were drawn as far away as possible from the tumor. Perfusion values of tumor(s), background liver, and spleen were then calculated averaging the functional parameters across all four sections. Functional maps (Fig 2) were displayed in colors ranging from blue to red, blue being the lower range of display for BF (color range, 0–400), BV (color range, 0–10), and PS (color range, 0–20) and red being the lower range of display for MTT (color range, 0–15) (Fig 1b). This was performed mainly to obtain comparable color maps.

A subspecialty-trained radiologist (D.V.S., with 11 years of experience in radiology and 5 years of experience in gastrointestinal radiology) interpreted these studies independently. Presence of angioinvasion was recorded on the basis of the criteria of thrombosis and enlargement of the portal or hepatic vein or inferior vena cava. Lack of thrombosis or presence of thrombosis

Figure 1



a. b.

Figure 1: **(a)** Transverse contrast material–enhanced CT image and **(b)** functional CT perfusion color map of BF demonstrate technique of CT perfusion in a patient with HCC in right lobe of liver. Various ROIs in aorta *(1)*, tumor *(2)*, normal liver *(3)* and spleen *(4)* were drawn. Functional color maps for each perfusion parameter were displayed according to color scale (large arrow), and average perfusion values for each ROI (small arrows) were obtained.

without enlargement of a vein was considered absence of angioinvasion. Clinical biomarker of HCC (serum α-fetoprotein level) and histopathology reports of tumor grade and presence of cirrhosis were gathered from patient electronic medical records by a radiologist (N.S.H.).

Statistical Analysis

Data were compiled in a database by using software (Access 2000; Microsoft, Redmond, Wash), and statistical analysis was performed with software (Excel 2000; Microsoft). One-way analysis of variance was used to compare the differences in CT perfusion parameters between tumor, background liver, and spleen and among different grades of HCC. In addition, analysis of variance was used to compare CT perfusion parameters of tumor and background liver in the presence or absence of cirrhosis and in the presence or absence of portal vein invasion. Spearman correlation coefficient was used to assess reproducibility of CT perfusion parameters and for comparison of CT perfusion parameters of HCC with clinical markers. A *P* value was calculated for each comparison, and a *P* value of less than or equal to .05 was considered to indicate a significant difference.

Figure 2

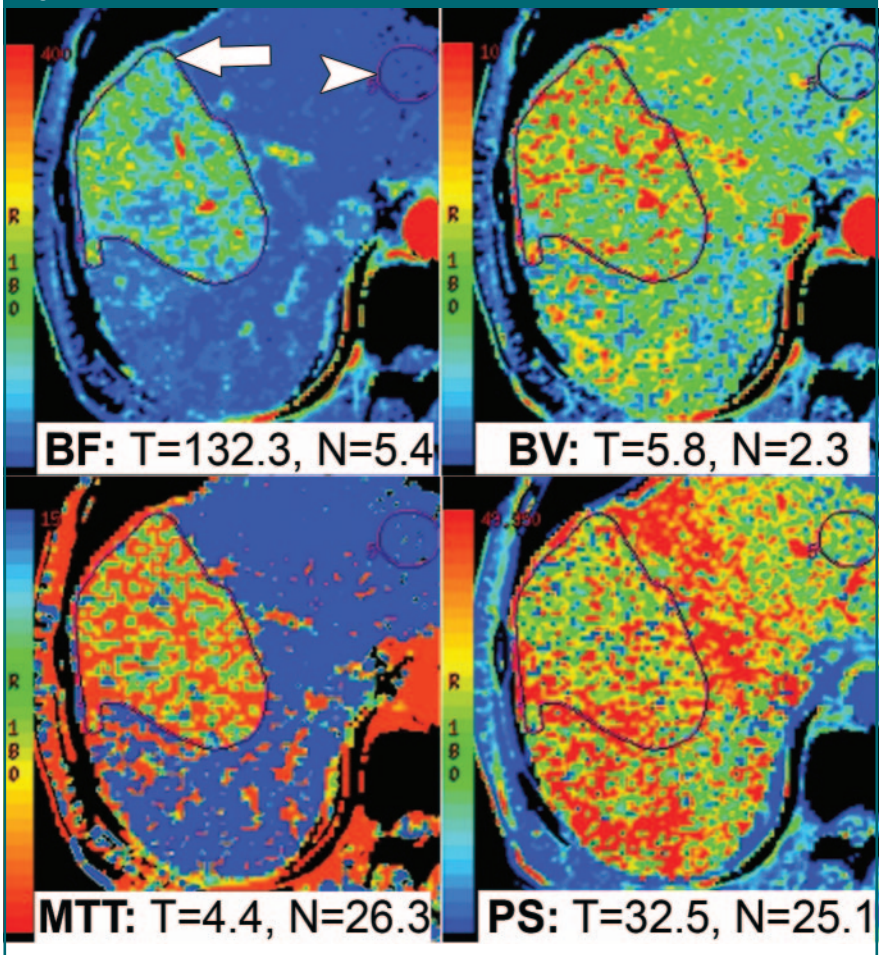


Figure 2: Transverse CT perfusion functional maps of BF, BV, PS, and MTT in 62-year-old man show large mass in right lobe of liver that has a distinct range of colors compared with background liver parenchyma. Perfusion values from ROI drawn for tumor *(T)* (arrow) and normal tissue *(N)* (arrowhead) show BF of 132.3 and 5.4 mL/100 g/min, BV of 5.8 and 2.3 mL/100 g, MTT of 4.4 and 26.3 seconds, and PS of 32.5 and 25.1 mL/100 g/min, respectively. Preferential arterial supply to HCC compared with dual vascular supply to liver results in higher BF, BV, and PS values and a lower MTT value in HCC, as shown in this example.

Results

In group A (n = 25) of our study cohort, the histopathologic distribution of HCC included well-differentiated (n = 9), moderately differentiated (n = 11), and poorly differentiated HCC (n = 5). Invasion of the portal vein was present at CT in nine (36%) of 25 patients. Concurrent invasion of the inferior vena cava was present in one of these nine patients, and invasion of the hepatic vein was present in two of these nine patients. Cirrhosis was present at histopathologic examination in 14 (56%) of 25 patients. Average size of HCC was 9.1 cm ± 3.8, with a range of 3.5–16.4 cm. In group B (n = 5), extrahepatic metastases were in the lung (n = 2), bone (n = 1), lymph node (n = 1), and peritoneum (n = 1); these metastases measured 3.5, 4.5, 3.0, and 8.2 cm, respectively.

Comparison of CT Perfusion Parameters between Primary HCC, Background Liver, and Spleen

Both spleen and HCC demonstrated higher CT perfusion parameters (BF, BV, PS) than background liver (Table 1). BF and BV of spleen were significantly higher than HCC and background liver in all cases; this reflects the high vascularity of the spleen. There was a significant difference in perfusion parameters between HCC and background liver ($P \leq .05$).

Reproducibility of CT Perfusion Parameters at Repeat Examination

For the four patients evaluated with regard to reproducibility of CT perfusion parameters, we obtained a high correlation (r = 0.9) with the first CT examination, with no significant variability (P = .01) at repeat examination (Fig 3). Mean tumor BF, BV, MTT, and PS, respectively, were 63.8 mL/100 g/min, 4.2 mL/100 g, 8.7 seconds, and 30.2 mL/100 g/min at first CT examination

and 59.3 mL/100 g/min, 4 mL/100 g, 9.1 seconds, and 28.5 mL/100 g/min at repeat examination. Mean variability of perfusion parameters was 4%. The least variable parameter was BF (1%), and the most variable parameter was PS (13%). BV and MTT demonstrated variabilities of 2.1% and 1.7%, respectively.

Table 1

CT Perfusion Parameters of Primary HCC, Background Liver, and Spleen

CT Perfusion Parameter	HCC	Background Liver	Spleen	*P* Value*
BF (mL/100 g/min)	92.8 ± 88.6	14.9 ± 2.8	124.9 ± 84	<.001
BV (mL/100 g)	4.9 ± 3.5	2.6 ± 0.9	5.8 ± 2.3	.004
MTT (sec)	8.1 ± 3.1	14.9 ± 2.3	6.2 ± 3.8	<.001
PS (mL/100 g/min)	34.5 ± 11.9	23.5 ± 8.2	40.9 ± 15.5	.001

Note.—Data are means ± standard deviations.

* A *P* value of ≤.05 indicates a significant difference between any two of the three regions (HCC, liver, or spleen).

CT Perfusion Parameters in Primary HCC

Mean BF, BV, and PS values were higher in well-differentiated HCC than in moderately or poorly differentiated tumors ($P < .05$). However, there was no significant difference in CT perfusion parameters between moderately and poorly differentiated HCC (Table 2).

Relatively higher and more variable perfusion parameters (BF, BV, and PS) were observed in nonangioinvasive HCC compared with those in angioinvasive HCC (Table 3). A significantly increased BF and BV was observed in the background liver of angioinvasive HCC compared with those observed in the background liver of HCCs without angioinvasion ($P < .001$). No differences in CT perfusion parameters were seen in either HCC or background liver when comparing cirrhotic with noncirrhotic livers (Table 3).

Relationship of CT Perfusion Parameters of Primary HCC with α-Fetoprotein

The median serum α-fetoprotein level was 4260 ng/mL (range, 6.5–164 100 ng/mL). We did not observe any statistically significant correlation between BF ($r = 0.3$, $P = .097$), BV ($r = 0.4$, $P = .7$), MTT ($r = -0.01$, $P = .95$), and PS ($r = 0.3$, $P = .13$) in primary HCC and serum α-fetoprotein levels in our study.

CT Perfusion Parameters in Extrahepatic Metastases

On assessing the vascularity of extrahepatic metastases present in the lung (Fig 4), lymph node, peritoneum, and bone (group B) by using CT perfusion (Table 4), we found relatively higher BF and BV values in metastases to the lung, bone, and peritoneum—values that were similar to average values for primary HCC in group A (BF = 92.8, BV = 4.9) (Table 1). However, lymph node metastasis demonstrated relatively lower BF and BV.

Discussion

CT perfusion is a feasible and, from our limited data, a reproducible technique for assessing tissue perfusion in locally advanced HCC. We observed significant differences between CT perfusion values of well-differentiated tumors and those of moderately and poorly differentiated tumors. CT perfusion imaging techniques are applicable to commercially available equipment currently installed in many imaging departments around the world. The introduction of multidetector CT has stimulated further interest in perfusion CT techniques and their future implementation in the clinical arena (6).

By using various approaches, investigators in the past have shown that contrast enhancement dynamics of a tissue can indirectly reflect the microenvironment of the tissue. Dugdale et al (13) have demonstrated correlation between higher tumor BF and higher grade of lymphoma at histopathologic examination. Similarly, Stevens et al (14) used dynamic CT for assessment of microvascular changes of tumor progression and demonstrated an increase in CT-derived BV and permeability with advancing age of VX2 tumors. In rectal cancer, a decrease in tumor vascularity at CT perfusion after radiation therapy was associated with a better response to therapy, whereas only a modest therapeutic response was observed in tumors with persistent vascularity (11). Results of another study on rectal cancer established a correlation between tumor BF at CT perfusion and microvessel density; this validates the use of CT perfusion in quantifying tumor angiogenesis (15). In addition, association between microvessel density and the degree of enhancement of HCC and renal cell carcinoma at CT has been previously demonstrated (16,17).

Our study results have demonstrated that CT perfusion values for the liver are reproducible, although our data are few. Stewart et al (18) have made similar observations with CT perfusion of liver tumors. We have also observed significant differences in CT perfusion parameters between HCC and background liver tissue. Well-differentiated HCC demonstrated relatively higher tumor BF, BV, and PS and lower MTT than did moderately and

Figure 3

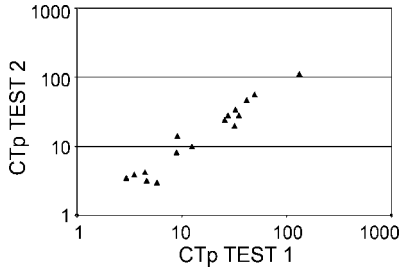


Figure 3: Graph of relationship of CT perfusion values (BF, BV, MTT, and PS) of HCC at initial CT perfusion *(CTpTEST1)* and repeat CT perfusion *(CTpTEST2)* shows reproducibility of the technique. Axes measure perfusion parameter values. Data points show perfusion parameters for each of the four patients.

Figure 4

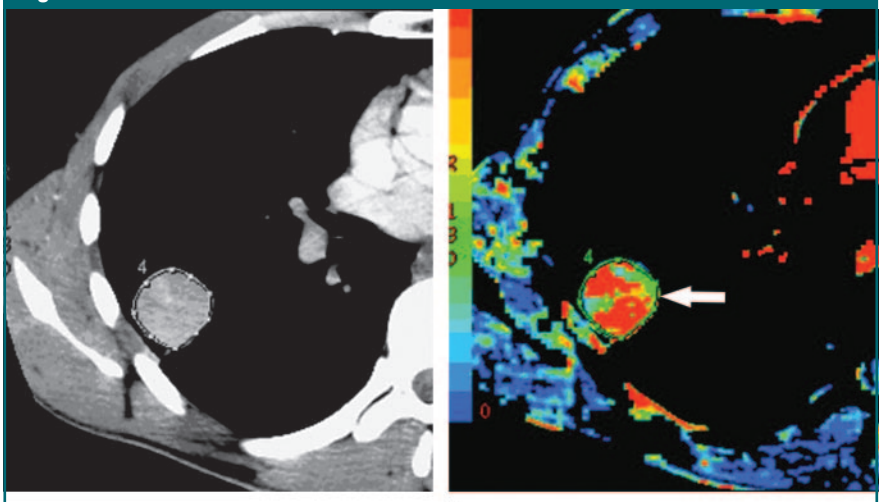


Figure 4: **(a)** Transverse contrast-enhanced CT image and **(b)** functional CT perfusion map of BF in 28-year-old man with lung metastasis (arrow) from HCC show high BF compared with adjacent muscle.

Table 2

CT Perfusion Parameters of Grades of HCC

Grade	BF (mL/100 g/min)	BV (mL/100 g)	MTT (sec)	PS (mL/100 g/min)
Well differentiated ($n = 9$)	173.4 ± 106.6	7.8 ± 4.5	5.8 ± 2.7	44.5 ± 13.3
Moderately differentiated ($n = 11$)	42.4 ± 14.6	3.1 ± 0.6	9.7 ± 2.1	27.9 ± 5.3
Poorly differentiated ($n = 5$)	58.1 ± 26.3	3.5 ± 0.6	8.7 ± 3.3	30.9 ± 7.4
P value*	.001	.003	.01	.002

Note.—Data are means ± standard deviations.

* A *P* value of ≤.05 indicates a significant difference between any two of the three grades.

poorly differentiated HCC. These observations stand in contrast to the conventional belief that high-grade tumors often derive increased vascularity. We believe that a relatively larger tumor diameter (mean, 9 cm) and presence of tumor necrosis in the high-grade tumor group could account for these observations.

There was also no significant difference in CT perfusion parameters of HCC when comparing patients with cirrhosis with those without and patients with tumor thrombus in the portal vein with those without. This observation further supports the ideas that hepatic arteries preferentially supply HCCs and portal vein thrombosis may not influence perfusion of HCCs. However, in patients with tumor thrombus in the portal vein, relatively higher BF and BV values were recorded in the background liver; we believe this may be because of increased portosystemic shunting of blood (19). PS and MTT of background liver were found to be comparable in patients with and those without angioinvasion. To our knowledge, there is no published study of the role of CT perfusion in HCC, although Wang et al (20) presented their data on CT perfusion of HCC and demonstrated higher BF, BV, and PS and lower MTT in HCC compared with the background liver—findings similar to those in our study.

The average perfusion values of metastases to the lung, bone, and perito-

Table 3

CT Perfusion Parameters of Primary HCC and Background Liver in Patients with and Those without Angioinvasion or Cirrhosis

	BF (mL/100 g/min)		BV (mL/100 g)		MTT (sec)		PS (mL/100 g/min)	
Parameter	Tumor	Background Liver	Tumor	Background Liver	Tumor	Background Liver	Tumor	Background Liver
Angioinvasion								
Present ($n = 8$)	62.5 ± 38.5	24.1 ± 16.7	3.5 ± 0.7	4.1 ± 4.7	8.3 ± 3.4	12.5 ± 2.9	30.7 ± 7.5	26.2 ± 17.6
Absent ($n = 17$)	107 ± 102.2	10.2 ± 6.6	5.5 ± 4.1	1.7 ± 1.1	8.0 ± 2.9	16 ± 5.9	36.2 ± 13.2	22 ± 18.9
P value	.25	.001*	.18	.007*	.83	.11	.28	.61
Cirrhosis								
Present ($n = 14$)	81 ± 73.1	18.3 ± 14.4	4.4 ± 2.4	3.2 ± 3.8	8.0 ± 3.1	13.4 ± 4.7	32.5 ± 9.6	21.6 ± 15.4
Absent ($n = 11$)	107.7 ± 107	10 ± 7.8	5.5 ± 4.5	1.9 ± 1.2	8.2 ± 3.1	17 ± 5.6	37 ± 14.2	26.1 ± 22.1
P value	.46	.11	.44	.22	.88	.1	.35	.56

Note.—Data are means ± standard deviations.

* Significant difference.

neum were found to be similar to those of HCC in the liver. However, lymph node metastasis demonstrated lower mean perfusion values. We are not sure if these observed differences are because of the tumor microenvironment at these sites or because of varying tumor burden. It is conceivable that the antiangiogenic response of the primary tumor and that of its metastases could be entirely different. Correlation between CT perfusion parameters and α-fetoprotein levels was not established in our study population.

There were a number of limitations to our study. First, the study sample size was small, and there was a selection bias because only patients with advanced HCC were included. It is possible that advanced HCC may have different perfusion patterns than early disease. Second, we did not perform any validation studies. CT perfusion parameters were not compared with the more established markers of angiogenesis, such as microvessel density or intratumoral interstitial pressure. Third, the criteria for tumor invasion of the portal vein and presence of metastases were based on imaging findings, and there was no histopathologic proof to confirm this claim.

Fourth, even though the liver has a dual arterial-portal blood supply, CT perfusion analysis was performed by using a single arterial input; the tumor and the portal vein could not be consistently included either because of the limited scanning range of 2 cm for CT perfusion or because of the presence of tumor thrombus in the portal vein. The likelihood of portal venous contribution in estimation of perfusion values is minimal because perfusion scanning was performed for less than 40 seconds after the initiation of contrast medium administration. However, this possibility cannot be entirely excluded. We believe that the recently introduced 64-section multidetector CT can offer greater coverage (up to 4 cm) and may potentially overcome this particular limitation by including both the tumor and portal vein in the scanning range for dual-input analysis. It is also essential to emphasize that these measured perfusion values are specific to our method of analysis.

Table 4

CT Perfusion Parameters of Extrahepatic Metastases from HCC

Site	BF (mL/100 g/min)	BV (mL/100 g)	MTT (sec)	PS (mL/100 g/min)
Lymph node ($n = 1$)	32	2.9	9	25.6
Peritoneum ($n = 1$)	81.6	3.5	4	21.8
Lung ($n = 2$)	128.9	5.1	4.5	39.8
Bone ($n = 1$)	112.4	6.5	8.5	50.2

Last, the radiation dose delivered to each patient with our CT perfusion technique was not assessed, although the estimated effective radiation dose (7.3–8.7 mSv), on the basis of the parameters used, was equal to that of a routine diagnostic abdominal CT study. Therefore, if CT perfusion were performed along with a diagnostic study, the patient would be exposed to an additional radiation dose.

Our initial experience suggests that CT perfusion is a feasible and, from our limited data, a reproducible technique for quantifying tumor vascularity and angiogenesis in advanced HCC. The perfusion parameters of well-differentiated HCC were found to be distinct from those of moderately and poorly differentiated HCC. The presence of cirrhosis or angioinvasion did not result in considerable alteration in tumor perfusion. No association between CT perfusion parameters and serum α-fetoprotein level could be established. In the future, CT-derived information about tumor perfusion may improve our understanding of tumor physiology and help to prognosticate patient outcomes, target treatment, and monitor response to novel therapies. It should be emphasized that our results are specific to the method of analysis and the software employed in this study.

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