Hypervascular Hepatocellular Carcinoma: Evaluation of Hemodynamics with Dynamic CT during Hepatic Arteriography

PURPOSE: To assess the hemodynamics and the main drainage vessel of hypervascular hepatocellular carcinoma.

MATERIALS AND METHODS: Single-level dynamic computed tomography during hepatic arteriography (CTHA) was performed in 32 patients with hepatocellular carcinoma. Carcinoma was confirmed with histologic (n = 9) or clinical (n = 23) examination results. Single-level CTHA findings were retrospectively analyzed. Histologic specimens from 40 livers with hepatocellular carcinoma were also examined, with special attention to vessels along the rim of the lesion.

RESULTS: Contrast material enhancement on single-level CTHA images occurred in four phases: (a) inflow of the contrast material into tumor, (b) tumor enhancement, (c) inflow of the contrast material into adjacent liver, and (d) corona enhancement of adjacent liver. Corona enhancement was seen in all lesions. A bright branching structure in the corona enhancement area, suggestive of a portal venule, was visible at the start of adjacent liver staining in 21 lesions. Continuity between a tumor sinusoid and a tiny vessel in the inner layer of the pseudocapsule was histologically confirmed in 10 of 40 specimens. Continuity between a tiny vessel in the inner layer and a portal vein in the outer layer of the pseudocapsule was confirmed with findings on serial sections from one liver.

CONCLUSION: The main drainage of hepatocellular carcinoma lesions may be a portal venule.

Understanding of arterial blood flow in neoplasms is important for radiologic interpretation, cancer research, and selection of the therapeutic strategy. Hepatocellular carcinoma (HCC) is one of the most common primary malignant neoplasms of the liver in the countries of the far East and southern Africa. The vascular architecture of HCC has been studied histopathologically (1-8). The hemodynamics of HCC have also been radiologically investigated for many years by using angiography (9), dynamic computed tomography (CT) (10,11), dynamic magnetic resonance imaging (MR imaging) (12,13), Doppler ultrasound (US) (14,15), and combined techniques such as CT during hepatic arteriography (CTHA) (16-18), CT during arterial portography (CTAP) (19,20), and US angiography (21). However, most investigations have been focused on the feeder vessels of HCC, and little has been reported about blood drainage of HCC in either the histopathology or radiology literature.

CT with slip-ring technology has made continuous scanning possible. This technology has been used mostly with helical CT, with which long cranio-caudal distances can be covered in a short time. Cine CT without table movement is another continuous scanning technique; it has been used for evaluation of lesion hemodynamics such as time-density analysis and dynamic movement of various lesions (22-24).

In the present study, we examined patients with hypervascular HCC by using both histologic specimens and single-level dynamic thin-section CTHA, which is a combination of thin-section CT with slip-ring technology and continuous scanning during and after the intraarterial injection of a small amount of contrast agent. The aim of this study was to...
assess the hemodynamics of hypervascular HCC and to determine the main drainage vessel of this tumor.

MATERIALS AND METHODS

Single-Level Dynamic CTHA

Single-level dynamic thin-section CTHA was performed in 32 patients (eight women, 24 men) with chronic liver disease who were suspected of having HCC. All 32 patients knew that single-level CTHA was part of an experimental protocol and gave informed consent. Patients with adenomatous hyperplasia of the liver or with a dysplastic nodule were not included in the present study. All 32 lesions (diameter, 9–53 mm; mean, 25 mm) had been detected with conventional CTHA performed immediately before single-level dynamic CTHA; all lesions were hyperattenuating. Histologic proof was obtained for nine lesions, and the remaining 23 lesions were clinically diagnosed. HCC was diagnosed on the basis of high levels of serum α-fetoprotein and/or proteins induced by vitamin K antagonist II; characteristic radiologic findings such as hypervascularity, presence of pseudocapsule, high signal intensity on T1-weighted MR images, and/or increase in size at follow-up imaging; and unfavorable clinical course. The pseudocapsule was visualized in 25 lesions either in a resected specimen or on radiologic images.

Angiography, CTAP, and conventional CTHA were performed before single-level dynamic CTHA. Celiac arteriography, selective hepatic arteriography, and superior mesenteric arteriography were initially performed with a digital subtraction angiographic technique. Before CTAP and CTHA, two sites of the same superficial femoral artery were punctured by using the Seldinger technique. After two 4-F angiographic catheters were positioned in the superior mesenteric artery for CTAP and in the common or proper hepatic artery for conventional and single-level dynamic CTHA, the patients were moved to the CT scanner. CTAP was performed first, followed by conventional CTHA. CTAP and conventional CTHA images that covered the entire liver were obtained, and the appropriate craniocaudal level for single-level dynamic CTHA was determined on the basis of CTAP and conventional CTHA images. In cases of multiple lesions, the largest lesion was selected for analysis. The total amount of contrast material used was less than 55 g of iodine. There were no complications due to the double puncture of the femoral artery.

Single-level dynamic CTHA was performed with the infusion of 10 mL of ioversol (Optiray; Mallinckrodt Medical, Montreal, Quebec, Canada) (320 mg of iodine per milliliter) at a rate of 1.0 mL/sec in the common or proper hepatic artery by using a power injector (Auto Enhance A-50; Nemoto Kyorindo, Tokyo, Japan). Scanning began immediately before initiation of the injection of contrast medium by using a HiSpeed Advantage scanner (GE Medical Systems, Milwaukee, Wis) with 1.0-second slip-ring technology. A 40-second (minimum) continuous scanning technique (180–220 mA, 120 kVp) without table feed was used to obtain sections with a thickness of 1 (n = 22) or 3 (n = 10) mm during a single breath hold. Oxygen was administered to patients to minimize discomfort at breath holding.

The images were reconstructed at 1-second intervals. Images were obtained with small field of view (9.6–16.0 cm²) targeted to the tumor of interest, and the “detail” reconstruction algorithm. The detail algorithm increases image resolution and image noise compared with the standard algorithm and decreases those parameters compared with the bone algorithm. Entire single-level dynamic CTHA images of each HCC lesion were displayed consecutively with the paging mode at the CT console by using a manual trackball.

Two experienced radiologists (K.U., O.M., Y.K.) reviewed the single-level CTHA images at the CT console. The time course of contrast enhancement and the transition of enhancement between the HCC lesion and adjacent liver on single-level CTHA images were interpreted. The time to enhancement of the lesion and adjacent liver and until the contrast medium was washed out of the lesion were also recorded. The readings were discordant in two patients in whom breath holding was rather poor; other readers then reviewed the images in these two patients, and a consensus was reached.
Histopathologic Examination

Specimens from 40 surgically resected cirrhotic livers with HCC lesions (diameter, 15–68 mm; mean, 32 mm) from the surgical file of recent cases at our laboratory were examined, including specimens from nine patients who underwent single-level dynamic CTHA. Each specimen was cut at the center of the lesion, fixed in 10% neutral formalin, and embedded in paraffin. More than 250 serial sections were obtained from one of the 40 liver specimens. The 3-μm thick sections were routinely stained with hematoxylin-eosin and with the elastic-van Gieson, Gomori silver, and azan-Mallory methods.

Histologic observation was focused on vessels along the rim of HCC lesions. The continuity between tumor sinusoid and intracapsular vessels was examined.

RESULTS

Single-Level Dynamic CTHA

The time course and the transition of contrast enhancement were classified in four phases (Figs 1, 2). (a) Immediately after injection of contrast material, inflow of the contrast material to the tumor was visualized, and intratumoral feeding arteries were clearly seen. This phase lasted 1–2 seconds. (b) The whole tumor was enhanced, and the contour of the tumor was clearly seen. This phase began 4.5 seconds ± 1.7 (mean ± 1 standard deviation) after the start of the injection. (c) Contrast enhancement of adjacent liver began 10.5 seconds ± 2.2 after the start of the injection. (d) The contrast material was washed out from the tumor, and corona enhancement of adjacent liver appeared. This phase began 22.4 seconds ± 6.1 after the start of the injection and lasted for the duration of scanning.

Corona enhancement was seen in lesions in all 32 patients, regardless of the presence of a pseudocapsule (Figs 1, 2). The enhancement was thick in places and projected into the surrounding liver in all lesions. These projecting parts contained a more hyperattenuating branching structure. This bright branching structure was visible at the start of adjacent liver staining in 21 (66%) lesions that were larger than 16 mm in diameter; three of these 21 lesions did not have a pseudocapsule. The branching structure suddenly appeared at the periphery of the tumor immediately before enhancement of the adjacent liver and did not directly connect with the intratumoral vessels. The branching structure gradually became isoattenuating with the corona enhancement. No vessels with an appearance of a hepatic vein that flowed together were depicted at the rim of HCC lesions. In all 32 lesions, a portal vein perfusion defect seen at CIAP correlated with the corona enhancement at single-level CTHA, which suggested that the portal venous blood supply from gut did not enter the area of the corona enhancement and that this area received blood that had passed through tumor sinusoids.

Histologic Examination

The HCC lesions in all 40 liver specimens were sinusoidal (trabecular) and had a pseudocapsule. There were no lesions with a sinusoidal growth pattern or a replacement growth pattern. The pseudocapsules comprised two layers: an inner layer rich in collagen fiber that was parallel to the contour of the tumor, like onion skin, and an outer layer that contained various numbers of compressed arteries and veins (Fig 3a). The thickness of both layers was uneven and was dependent on the size of the lesion; larger lesions had a thicker pseudocapsule. The outer layer also contained abundant collagen fiber. The outer layer differed from the inner layer, however, because the former contained vessels large enough (diameter > 20 μm) to be recognized at low magnification. These recognizable vessels marked the boundary between the two layers. At higher magnification, some slitlike gaps that contained red blood cells were seen between collagen fibers in the inner layer and were thus defined as vessels (Fig 3b). Some veins in the outer layer were accompanied by bile ducts and were thus defined as portal veins (Fig 3a). Therefore, the pseudocapsule contained rather large vessels in the outer layer and a large number of tiny, slitlike vessels in the inner layer.

The continuity between tumor sinusoid and tiny vessels in the inner layer was clearly recognizable in 10 (25%) of the 40 HCC lesions (Fig 3b). In the specimens from which more than 250 serial sections were cut, the continuity among tumor sinusoid, a tiny vessel in the inner layer, and a portal venule in the outer layer was demonstrated (Fig 4).

DISCUSSION

Our results demonstrated the blood drainage of HCC lesions dynamically on single-
level dynamic CTHA images and statistically in histologic specimens (including serial sections). At single-level dynamic CTHA, we observed that the blood entered the lesion via the hepatic artery, spread throughout the lesion, flowed into the portal venule in the adjacent liver, and then spread into the surrounding liver. At histologic examination, the connection between tumor sinusoid, small vessels in the inner layer of the pseudocapsule, and a portal venule in the outer layer of the pseudocapsule was confirmed.

Single-level dynamic CTHA, which is a new method to delineate the blood flow in hepatic neoplasms, depicts the blood drainage passing through the portal venule from the tumor to the surrounding liver, as well as the blood supply from the hepatic artery. The technique is a combination of thin-section CT with slip-ring technology and continuous scanning during and after intraarterial injection of a small amount of contrast medium. A slip-ring CT scanner allows continuous scanning of the lesion, which increases the temporal resolution of the images and demonstrates blood flow in and out of the tumor. This CT technique with thin collimation and a small area of interest results in excellent spatial resolution, and its advantages for evaluation of fine structures such as temporal bone (25) and peripheral lung (26) have been well demonstrated. We demonstrated the capabilities of this technique in imaging of the liver, especially portal venules in the surrounding liver; to our knowledge, the use of this CT method has not been reported in the abdominal region except for imaging in the appendix (27). Continuous scanning after intraarterial injection of a small amount of contrast material also depicted washout of the contrast material from the tumors.

It has been reported (1,9,28) that blood supply to HCC lesions is mainly via the hepatic artery. The drainage of HCC lesions is thought to be via the portal or hepatic vein (29–31). However, little has been reported about this issue, and the main drainage vessel of HCC lesions has not, to our knowledge, been clearly demonstrated. We are not aware of any histopathologic descriptions of continuity between a tumor sinusoid and an intracapsular vessel. One of the reasons is that the connection between a tumor sinusoid and an intracapsular vessel is seldom seen on routinely stained histologic sections. Another reason is that the small vessels in the inner layer of the pseudocapsule have not been considered to be the efferent vessels of HCC lesions. Nakashima and Kojirō (1–3) reported that colored gelatin injected into portal veins in an autopsy specimen was observed only at the boundary of the HCC lesion, and there was no description of the continuity between a portal vein and tumor in their pictorial atlas (3). Kita et al (29) confirmed the connection between tumor sinusoid and portal vein by using methacylate resin injected in both the hepatic artery and portal vein and scanning electron microscopy. However, they interpreted the portal vein to be one of the efferent vessels of HCC lesions and did not refer to the positional relevance of the portal vein and pseudocapsule. It is possible that the connection between tumor sinusoid and intracapsular portal vein was not demonstrated with the colored-gelatin-injection method because the gelatin was too viscous to pass through the small vessels in the inner layer of the pseudocapsule. On the other hand, the resin can pass through these small vessels and demonstrate the continuity between tumor sinusoid and portal vein. However, the direction of blood flow—whether the portal vein is afferent or efferent—cannot be clarified by using the method of Kita et al.

Our results suggest that the portal vein is the main drainage vessel of HCC. At single-level dynamic CTHA, the hyperattenuating branching structure appeared after the tumor had enhanced at the rim. This bright branching structure was located at the periphery of the lesion and
received contrast medium from the lesion, which suggests that this structure is the drainage vessel of HCC. Just after this branching structure appeared, the adjacent liver around this structure began to enhance; that is, the contrast medium in the branching structure flowed into the liver. Thus, we suggest that this branching structure is a feeder vessel to the liver, namely, a portal venule.

The connection between tumor sinusoid and portal vein in the outer layer of the pseudocapsule was observed at histopathologic examination, although a limitation of our study was that serial sections were obtained in only one specimen. Although our histologic observation could not demonstrate the direction of blood flow, the in vivo single-level dynamic CTHA findings provided evidence of the direction of blood flow, which correlated with the histologically observed connection between tumor sinusoid and portal vein in the pseudocapsule.

An important question is whether drainage in the seven HCC lesions that did not have a pseudocapsule is also via portal venules. Some nonencapsulated HCC lesions have been reported (32) to show a sinusoidal or replacement growth pattern, with a hepatic sinusoid directly connected to a tumor sinusoid and thought to be both a feeding and a drainage vessel. The hepatic sinusoid is located between the tumor sinusoid and portal vein in such cases, and the blood may drain from tumor directly into the hepatic sinusoid rather than into the portal vein. In the present study, three of the seven HCC lesions without a pseudocapsule had a hyperattenuating branching structure in the area of corona enhancement, and the remaining four HCC lesions had thick parts of corona enhancement that projected into the surrounding liver, which suggests that a part of the blood drains into portal venules from the HCC lesion in vivo. The blood may flow into the portal vein via hepatic sinusoids in a retrograde manner by following a pressure gradient. However, we did not histologically examine any specimens with nonencapsulated HCC lesions, and further studies are needed to determine how the blood drains from nonencapsulated HCC lesions.

Another important question is why the continuity between tumor sinusoid and tiny vessels in the inner layer was seen in only 10 (25%) specimens. There are three
reasons for this. First, the continuity is actually present in only a small proportion of HCC lesions. Second, the number of sections per lesion observed in the present study was too small (one section per lesion) to detect the continuity. Third, the continuity is difficult to recognize on routinely stained sections. The real number of cases with continuity can be estimated when the entire lesion is cut and stained with immunohistochemical and/or lectin histochemical methods (ie, blood group antigens, Ulex europaeus agglutinin I, human hematopoietic stem cell and endothelial cell marker CD34, and factor VIII-related antigen). However, further examination is needed and the actual number of cases with continuity remains unknown.

It is interesting that HCC drainage began in a vessel that was small (Figs 3, 4) compared with the diameter of the feeding artery. This finding is relevant to the reason why the drainage vessel has gone unrecognized both on radiologic images and in histologic specimens. This finding may also be relevant to the accumulation of the embolic agent for transarterial embolization (eg, with iodized poppy seed oil) of HCC lesions, especially the encapsulated type: The embolic agent may not be able to pass easily through the tiny drainage vessel despite being able to pass easily through the feeding artery.

The clinical usefulness of single-level dynamic CTA is questionable at the moment. We think that the precise blood flow information obtained with single-level CTA may be useful for the differential diagnosis of various hepatic lesions. We did not, however, obtain verification of the usefulness of this technique for differential diagnosis, and further study is needed as regards this issue.

In conclusion, we believe that the main drainage vessel of encapsulated HCC lesions is the portal venule. The blood drains into the surrounding liver through tiny vessels in the inner layer of the pseudocapsule, the portal vein in the outer layer (which was confirmed with histologic results), and a portal venule in the adjacent liver (which was confirmed with single-level dynamic CTA findings). The results we obtained would be helpful for radiologic interpretation, for hepatologic questions such as the reason why portal venous tumor thrombus is more frequent than hepatic venous thrombus, and for improvement of a therapeutic strategy such as transarterial embolization. However, because of the limitations of our study already mentioned, further investigation is necessary and is in progress.

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References