ORIGINAL ARTICLE

Correlation of dynamic multidetector CT findings with pathological grades of hepatocellular carcinoma

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PURPOSE
Our objective was to examine whether different vascularization patterns seen during three phases of dynamic multidetector computed tomography (MDCT) of the liver correlated with the histopathological differentiation findings of hepatocellular carcinoma (HCC) in chronic liver disease patients.

MATERIALS AND METHODS
Dynamic MDCT images from 46 patients (38 males and 8 females; ages between 1 and 90 years; mean age, 53) pathologically diagnosed with HCC were retrospectively evaluated. Lesions were divided into three groups according to MDCT enhancement patterns. Pathologically determined differentiation degrees were compared with contrast enhancement patterns in the hepatic arterial, portal venous, and hepatic venous phases.

RESULTS
Lesion characterization was as follows: Type 1 (6 patients), hypoattenuating in the hepatic arterial and hepatic venous phases and hyperattenuating in the portal venous phase; Type 2 (10 patients), hypoattenuating in all phases; and Type 3 (30 patients), hyperattenuating in the hepatic arterial and portal venous phases and hypoattenuating in the hepatic venous phase. Patients were pathologically classified as having either well-differentiated (n=32) or poorly differentiated HCC (n=14). All patients with poorly differentiated HCC had a Type 3 enhancement pattern. All patients with Type 1 and 2 enhancement patterns had well-differentiated HCC. There was a significant correlation between pathological differentiation degrees and radiological enhancement (P = 0.003).

CONCLUSION
Dynamic MDCT revealed that poorly differentiated HCC patients all had hypervascular enhancement patterns, and hypovascular-type enhancement was present in all patients with well-differentiated HCC. Imaging patterns of dynamic MDCT scanning in HCC patients may be helpful for follow-up examinations and for determining clinical prognosis.

Key words: • carcinoma, hepatocellular • tomography, spiral computed • diseases, liver

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Hepatocellular carcinoma (HCC) is a malignant liver neoplasm characterized by nodular lesions that are usually observed in cirrhotic livers. It is most frequently seen between the fifth and seventh decades of life (1, 2). The increasing incidence of HCC is a result of hepatitis C infections and the prolonged life spans of cirrhosis patients. Increases in hepatitis B infections, alcoholic liver disease, tyrosinemia, and hemochromatosis have also caused the HCC incidence to rise. Additional risk factors include increased androgen levels, α1-antitrypsin deficiency, exposure to aflatoxins and the use of oral contraceptives. The growth of HCC is usually silent; the disease may not be diagnosed for up to three years. The average lifespan of patients after diagnosis is five years (1).

Pathologically, HCC is classified into well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated types (3–6), and the pathological differentiation of an HCC lesion plays an important role in determining the patient's prognosis (2, 3).

The advent of recent developments in computed tomography (CT) makes it possible to obtain information about a lesion's hemodynamic features. Dynamic multidetector CT (MDCT) provides data about tumor vascularization in the hepatic arterial, portal venous and hepatic venous phases, and it can be used to separate hypervascular from hypovascular lesions. There are only a limited number of studies on a small number of HCC patients that have compared the pathological differentiation degrees to dynamic CT and CT angiography findings (2, 4, 7, 8).

The main purpose of our study was to determine whether the various vascularization patterns of HCC nodules observed during the three phases of dynamic liver MDCT correlate with histopathological differentiation grades. If so, this technique could be used to obtain advanced information about the differentiation degrees of lesions in newly diagnosed patients, and changes in lesion differentiation in diagnosed patients could be non-invasively tracked without the need for a second biopsy.

Materials and methods

Patient group

The study included 46 patients with a pathological diagnosis of HCC who also had undergone a dynamic MDCT scan in our hospital between October 2000 and November 2007. All of the images were retrospectively evaluated by two radiologists with 5 and 10 years of experience in abdominal imaging who did not know the pathological grade. All of the images were evaluated by the two radiologists together and determinations were made by consensus. The patients included 38 males and 8 females aged between 1 and 90 years (mean age, 53 years). Lesion sizes were between 0.7 and 13.5 cm (mean lesion size, 3.64 cm). The contrast

enhancement patterns of lesions were evaluated in the hepatic arterial, portal venous and hepatic venous phases and compared with the pathological degrees of differentiation determined histopathologically by an experienced pathologist.

MDCT protocol

First, 5-mm thick precontrast images were obtained. After injecting an approximate total dose of 20 to 150 mL non-ionic iodinated contrast material with a concentration of 1.5 to 2 mL/kg via an automated injector (MEDRAD, Vistron CT® Injection System, MedRad, Indianola, Pennsylvania, USA) as a bolus, images were obtained using a 4- or 16-detector dynamic MDCT (Volume Zoom, Sensation 16, Siemens, Erlangen, Germany). Contrast material was administered at a rate of 3.5 mL/s. The rotation time was 0.5 s, and the pitch was 1.3. Section thickness was set to 5 mm, and collimation was set to 1.5 mm while taking the images. Every phase was obtained during a period of approximately 16 to 20 s while the patient held their breath. From the beginning of contrast injection, the hepatic arterial phase images were obtained 15 to 25 s later, the portal venous images were obtained 65 s later and the hepatic venous phase images were obtained 5 min later. Our institutional review board granted approval for the retrospective evaluation of patients' records and images. No informed consent was needed for this retrospective study.

Image interpretation

By comparing the attenuation degrees of the lesions to the hepatic parenchyma surrounding them, we evaluated the imaging patterns of the lesions as either hypoattenuating, isoattenuating, or hyperattenuating. Lesions larger than 3 cm generally displayed necrosis at their center, and they were evaluated based on the exterior areas of the lesions.

All of the lesions were grouped based on imaging patterns in the hepatic arterial, portal venous, and hepatic venous phases. There were three types of enhancement patterns observed, and they were grouped accordingly. Compared to the surrounding hepatic parenchyma, the following imaging pattern types were observed: Type 1, hypoattenuating in the hepatic arterial and hepatic venous phases and hyperattenuating in the portal venous phase; Type 2, hypoattenuating in all phases; and Type 3, hyperattenuating in the hepatic arterial and portal venous phases and hypoattenuating in the hepatic venous phase. In addition to these types, lesions that were iso-attenuating compared to the hepatic parenchyma in the hepatic venous phase but displayed washout patterns compared to the portal venous phase were considered to be hypoattenuating lesions.

The patients' records were also reviewed for follow-up data and grouped according to MDCT type.

Pathological examination

A pathologist experienced with liver pathologies examined all 46 nodules of the resected specimens with no knowledge of the pre-operative or prebiopsy MDCT findings. Differentiation degrees of the cancer cells were classified according to the World Health Organization criteria (9). Pathologically, HCC is classified into well-differentiated (Grade 1), moderately differentiated (Grade 2), poorly differentiated (Grade 3), and undifferentiated (Grade 4) types. Only one of our patients was determined to be Grade 1, and only one was established as Grade 4. Due to the paucity of patients with Grade 1 or 4 tumors, the pathological groups were divided into two categories: the first two grades (Grades 1 and 2) were considered to be well-differentiated, and the last two grades (Grades 3 and 4) were considered to be poorly differentiated HCC.

Statistical analysis

All statistical calculations were performed using a computer software (Statistical Package for Social Sciences version 11.0, SPSS Inc., Chicago, Illinois, USA). The evaluated parameters included radiological imaging patterns and pathological differentia- tion degrees. The chi-square test was planned to be used to identify any significant relationships between radiological types and pathological grade distribution. However, the chi-square test conditions could not be provided, therefore, a Monte Carlo exact test was used to interpret the results. A *P* value < 0.05 was accepted as statistically significant.

Results

According to the dynamic MDCT results, there were 6 patients in the Type 1 group (Fig. 1), 10 patients in the Type 2 group (Fig. 2) and 30 patients in the Type 3 group (Fig. 3). With respect to pathological grading, as discussed above, 32 patients had well-differentiated HCC (Grades 1 and 2), and 14 patients had poorly differentiated HCC (Grades 3 and 4). The distribution of MDCT types according to pathological grade is shown in Table.

All patients who showed a hypovascular-type enhancement pattern (Types 1 and 2) were in the well-differentiated pathology group. A hypervascular-type enhancement pattern (Type 3) was observed in both the well-differentiated and the poorly differentiated HCC groups. The only patient with Grade 1 HCC had a Type 2 (hypovascular) enhancement pattern, and all other patients in the well-differentiated group had moderately differentiated HCC. All patients with poorly differentiated HCC showed a Type 3 hypervascular enhancement pattern. There were significant differences in pathological grade percentages between the groups (*P* = 0.003). In the Type 3 enhancement pattern group, 53.3% were well-differentiated HCC and 46.7% were poorly differentiated HCC, and all the patients in the Type 1 and 2 hypovascular enhancement pattern groups had well-differentiated HCC (Fig. 4).

On follow-up of the Type 1 patients, three patients who had no treatment

Table. The distribution of dynamic MDCT contrast enhancement types according to pathological grades of HCC lesions

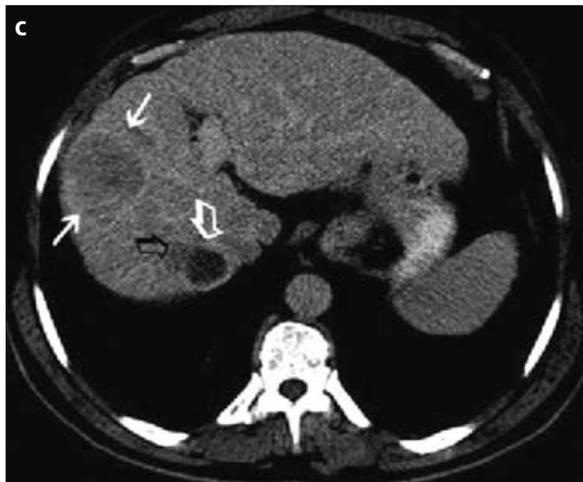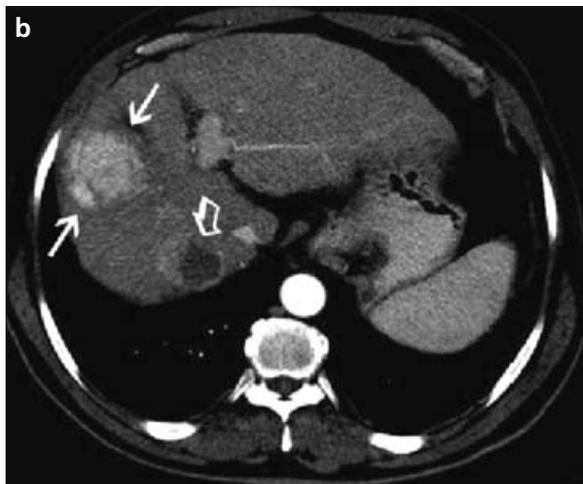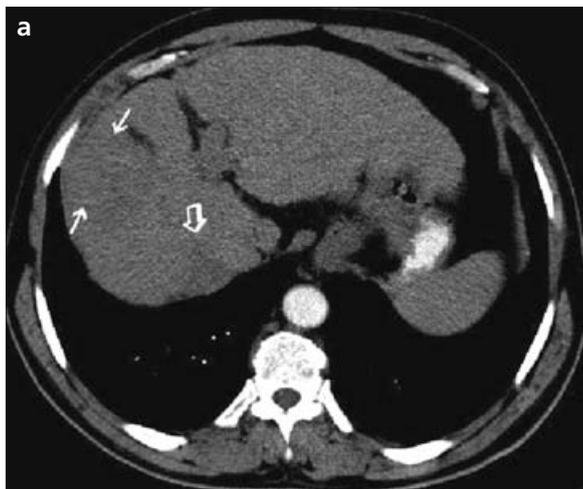| Pathological grading	Dynamic MDCT types			Total
	1	2	3	
Well-differentiated HCC	6	10	16	32
Poorly differentiated HCC	0	0	14	14
Total	6	10	30	46

Figure 1. **a–c.** A 63-year-old man pathologically diagnosed with well-differentiated HCC; Type 1 enhancement pattern on dynamic MDCT. There are two nodular lesions in segment VII and segment VIII of the liver. The lesions are hypoattenuating on the hepatic arterial phase compared to the parenchyma (*arrows and open arrow,* **a**).The contrast enhancement of the lesion in segment VIII of the liver is significant compared to the parenchyma in the portal venous phase (*arrows,* **b**). The second lesion in segment VII exhibits the same peripheral enhancement pattern and a central necrotic area (*open arrow,* **b**). The lesions show washout and hypoattenuation compared to the parenchyma in the hepatic venous phase (*arrows and black open arrow,* **c**). Also shown is the necrotic area (*white open arrow,* **c**).

Figure 2. **a–c.** A 13-year-old girl pathologically diagnosed with well-differentiated HCC; Type 2 enhancement pattern on dynamic MDCT. There is a 4-mm lesion in segment VIII of the liver. Hypoattenuating lesion in the hepatic arterial phase (*arrows,* **a**). Hypoattenuating lesion in the portal venous phase (*arrows,* **b**). Hypoattenuating lesion in the hepatic venous phase (*arrows,* **c**).
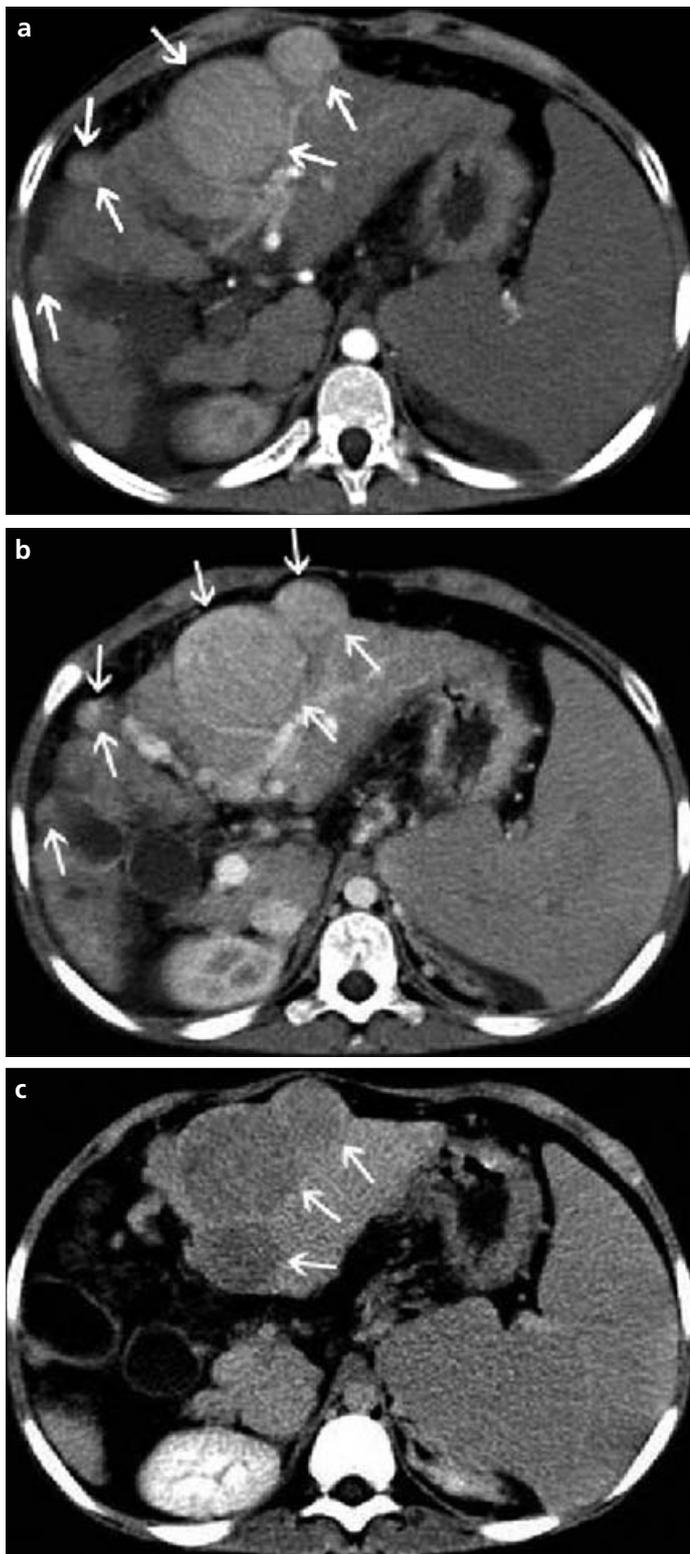
Figure 3. a–c. A 15-year-old boy pathologically diagnosed with poorly differentiated HCC; Type 3 enhancement pattern on dynamic MDCT. There are multiple exophytic mass lesions in segments IV and VIII of the liver. Hyperattenuating lesions compared to the parenchyma in the hepatic arterial phase (*arrows,* **a**). Hyperattenuating lesions in the portal venous phase (*arrows,* **b**). Hypoattenuating lesions with significant washout in the hepatic venous phase (*arrows,* **c**).

died within three years, one received chemoembolization treatment and is living and two patients were lost to follow-up. Of the Type 2 patients, three received an orthotopic liver transplant and are living disease-free, three received local treatment (chemoembolization and alcohol injection) and are living, two died without treatment, and two were lost to follow-up. Of the Type 3 patients, eight died within six months after their diagnosis, six had an orthotopic liver transplantation and are living, three who had surgical excision or transplantation had a recurrence of the disease, three who received transplants died in the early post-operative period because they were a Child's C grade and had post-operative complications, five were lost to follow-up and five had chemoembolization or partial resection and were followed up for two to four years. The patient who had Grade 1 well-differentiated HCC is living disease free three years after chemoembolization. The three patients who were lost to follow-up after transplantation surgery, six of the patients who died within six months and the three who had recurrent disease were all in the poorly differentiated group. The remaining two patients in the poorly differentiated group received an orthotopic liver transplant and are living.

Discussion

New vessel formation in an HCC lesion plays a critical role in tumor growth and metastasis. The primary tumor size of an HCC lesion and the status of metastasis are crucially important to prognosis and treatment (1). During hepatocarcinogenesis, first arterial and then portal blood flow decreases. Because of the reduced arterial blood flow, the formation of new arterial vessels increases, and this causes hypervascular lesions to occur. Thus, a decrease in a tumor's pathological differentiation degree is accompanied by new vessel formation (2, 4). As a result, the vascularization degree of HCC is important for the prognosis and treatment of the disease.

Conventional angiography is considered to be the gold standard for demonstrating the vascularity of HCC lesions, and the only way to determine the pathological grade of a lesion is *in vitro* evaluation of material obtained either by surgery or biopsy. This type of grad-
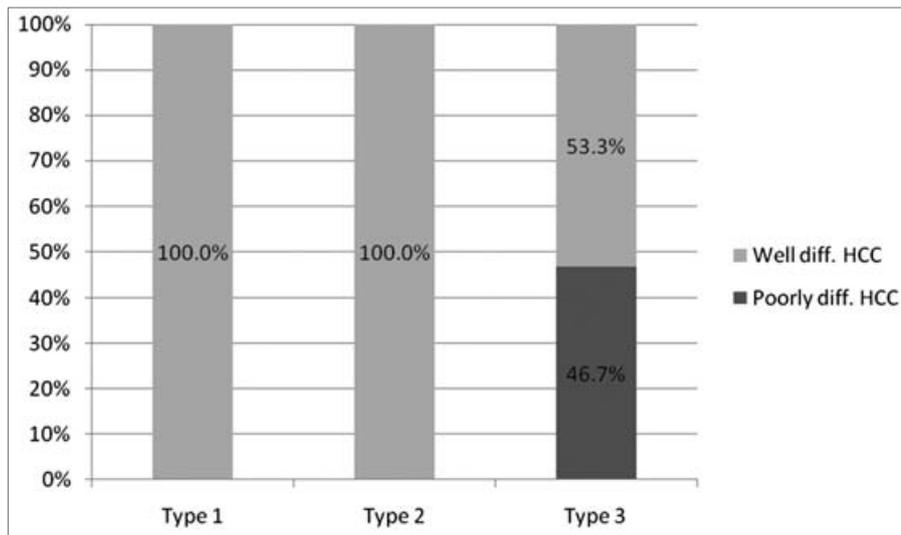
Figure 4. Distribution of percentages of pathological grades. diff. HCC, differentiated hepatocellular carcinoma

ing means that only invasive methods are currently used to track prognosis. In various studies, complication rates after a liver biopsy in cirrhotic patients have ranged from 0.8% to 3.6% for major complications and 2.3% to 39% for minor complications (10). Because of the fragility of the pathological vessels formed during hepatocarcinogenesis, the risk of complications in HCC patients due to invasive techniques is probably even higher than these numbers suggest (11). Today, new methods, such as MDCT, that can accurately show hemodynamic changes are commonly used in these patients. As a fast and non-invasive imaging method, MDCT allows patients to be examined in a short time with easily tolerated breath-holding phases. When performed dynamically, MDCT provides more information about tumor vascularization than do conventional techniques and can also help differentiate its pathological grade non-invasively, as shown by our study.

The treatment of HCC, which has a significant mortality rate if left untreated, is of great importance. The vascularization and the pathological differentiation grades of HCC are crucial during follow-up because they affect the prognosis and survival rate. Today, liver transplantation is considered the most effective treatment for HCC. Previous studies have shown that after orthotopic liver transplantation, the 1-year survival rate is 98% and the 5-year survival rate is 90% (12). When left untreated, the five-year survival rate in patients with HCC is less than 5%. The pathological grade and vascularization of the tumor determine the risk of metastasis, thereby necessitating chemotherapeutic agents in addition to surgery in some cases (1). Some investigators have previously reported a correlation between histopathologic grade and blood supply to the HCC in radiological and pathologic analyses. These researchers mainly focused on precancerous lesions and early-stage HCC (4, 13). However, few previous reports have examined the vascular changes that occur in the late stage of the disease and the direct relationship between arterial blood flow to the tumor and the tumor's proliferative activity (4, 7). Previous researchers that have compared pathologic differentiation degrees with MDCT findings have all performed CT hepatic arteriography and CT arterial portography, which are invasive techniques. The primary purpose of our study was to compare non-invasive MDCT findings in arterial and portal phase imaging with degrees of pathologic differentiation.

This study reveals that there is a significant relationship between the pathological grades of HCC lesions and their radiological enhancement patterns revealed by dynamic MDCT. The Type 3 MDCT enhancement patterns found in all of the poorly differentiated HCC lesions indicate that these lesions have greater arterial vascularization than well-differentiated lesions. The results of our study are consistent with previous reports (5, 14). We found Type 3 enhancement patterns in the well-differentiated HCC group, which mostly included moderately differentiated HCCs. The presence of arterial hypervascularization in all of the poorly differentiated HCCs and some of the moderately differentiated HCCs indicates that lesions with this contrast enhancement pattern are most likely at a late pathological stage or an advanced-to-late stage, thereby providing clinicians with important, non-invasively obtained information that can help determine treatment options.

Even though HCC is usually considered to be a hypervascular tumor, well-differentiated tumors can be hypovascular. All Type 1 and Type 2 lesions that had hypovascular enhancement patterns in this study were well-differentiated. Although Type 1 lesions showed enhancement in the portal venous phase and some washout in the hepatic venous phase, they were relatively hypovascular compared to the Type 3 lesions. Type 1 lesions did not show arterial hyperattenuation. A Type 2 contrast enhancement pattern was seen in the only patient who had pathologically Grade 1 (well-differentiated) HCC. Half of the patients with moderately differentiated HCCs (Grade 2) had Type 1 or 2 contrast enhancement patterns, whereas the other half had Type 3. When arterial hypervascularization is exhibited, new vessel formation may have begun even though the lesion is moderately differentiated. None of the patients with poorly differentiated HCC showed Type 1 or Type 2 enhancement patterns.

In the Type 1 enhancement pattern, although there was no arterial hypervascularization, the lesions showed some washout in the late venous phase, but in the Type 2 hypovascular enhancement pattern, there was no washout. Thus, it is not always possible to differentiate Type 2 lesions from other benign lesions, such as regeneration nodules, although most benign lesions are hyperintense or isointense to the liver in the hepatic venous phase. This difficulty in differentiation may be a problem if the patient is examined for the first time with MDCT and without a previous biopsy. In these patients, clinical findings such as α-fetoprotein elevation may help with differentiation.

We also found that none of the patients showed hyperattenuating le-

sions compared to the parenchyma in the hepatic venous phase. There were a few patients who had isoattenuating lesions, but because they showed a decrease in attenuation compared to the portal venous phase, they were grouped as a Type 1 enhancement pattern. This type of enhancement provides further evidence that benign lesions typically show hyperattenuation in the hepatic venous phase; all of our patients had malignant pathology, and none of the HCC lesions imaged were hyperattenuating in the hepatic venous phase.

On follow-up examination, we observed that most of the patients who had died and all of the patients who had a recurrence after treatment (surgical resection and transplantation) demonstrated a Type 3 enhancement pattern and were in the poorly differentiated pathology group. This also reveals that, in patients with Type 3 enhancement patterns, the prognosis is worse for the poorly differentiated group.

The greatest limitation of this research was the small number of patients. The most important reason for this was the lack of a biopsy in all patients with liver lesions; thus, the pathological diagnoses could not be determined (the patients that had no pathology were not included in the study). In addition, the number of patient groups distributed according to pathological differentiation grades was insufficient. There was only one patient with Grade 1 and one with Grade 4 lesions; because statistical analyses could not be performed on those single patients, they were added to the other grades. The poorly differentiated group also contained fewer patients than the well-differentiated group. As a result, more studies with larger patient groups are needed for further analysis of dynamic imaging patterns in poorly differentiated HCC patients. Another limitation of the study was that we obtained arterial phase images in the early

arterial phase. Although we obtained a late arterial phase image immediately after the first one for patients in whom we observed no enhancement of the arterial vascular structures, because of the retrospective nature of the study, we may have missed arterial enhancement in some patients. Late arterial phase scanning can be added to image patients with hepatic nodules in the context of cirrhosis.

In conclusion, this research reveals that radiological imaging patterns of non-invasive dynamic MDCT in HCC patients are important for diagnosis, follow-up and determination of clinical prognosis. According to the contrast enhancement pattern of nodules seen on dynamic MDCT, treatment options can be evaluated in regards to prognosis with the knowledge that arterial neovascularization is seen more in hypervascular lesions. We observed that all patients who had hypovascular enhancement (Types 1 and 2) had well-differentiated HCC. Thus, when a Type 1 or Type 2 enhancement pattern is observed on dynamic MDC, and if the lesion is HCC, we can consider it to be well-differentiated HCC. Furthermore, a change in the enhancement pattern with dynamic MDCT that shows an increase in arterial vascularization during follow-up examination may indicate an increase in the pathological grade, and the patient can be evaluated according to this change without the need for repeat biopsies.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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