Hepatocellular carcinoma in cirrhotic patients at multidetector CT: hepatic venous phase versus delayed phase for the detection of tumour washout

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Objectives: Our aim was to compare retrospectively hepatic venous and delayed phase images for the detection of tumour washout during multiphasic multidetector row CT (MDCT) of the liver in patients with hepatocellular carcinoma (HCC).

Methods: 30 cirrhotic patients underwent multiphasic MDCT in the 90 days before liver transplantation. MDCT was performed before contrast medium administration and during hepatic arterial, hepatic venous and delayed phases, images were obtained at 12, 55 and 120 s after trigger threshold. Two radiologists qualitatively evaluated images for lesion attenuation. Tumour washout was evaluated subjectively and objectively.

Tumour-to-liver contrast (TLC) was measured for all pathologically proven HCCs.

Results: 48 HCCs were detected at MDCT. 46 of the 48 tumours (96%) appeared as either hyper- or isoattenuating during the hepatic arterial phase. Subjective washout was present in 15 HCCs (33%) during the hepatic venous phase and in 35 (76%) during the delayed phase ($p < 0.001$, McNemar's test). Objective washout was present in 30 of the 46 HCCs (65%) during the hepatic venous phase and in 42 of the HCCs (91%) during the delayed phase ($p = 0.001$). The delayed phase yielded significantly higher mean TLC absolute values compared with the hepatic venous phase (-16.1 ± 10.8 HU vs -10.5 ± 10.2 HU; $p < 0.001$).

Conclusions: The delayed phase is superior to the hepatic venous phase for detection of tumour washout of pathologically proven HCC in cirrhotic patients.

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Multiphasic contrast-enhanced multidetector row CT (MDCT) plays a pivotal role in the diagnostic work-up of cirrhotic patients, who are at increased risk of developing hepatocellular carcinoma (HCC) [1]. Increased enhancement of the tumour compared with the surrounding liver parenchyma during the hepatic arterial phase is the cornerstone for the diagnosis of HCC at multiphasic MDCT [1, 2]. However, a variety of entities—dysplastic nodules [3], confluent hepatic fibrosis [4], non-tumourous arterioportal shunts [5] and haemangioma [6]—can also manifest with increased arterial enhancement and thus mimic HCC, particularly if they are smaller than 2 cm in diameter.

Tumour washout, *i.e.* hypoattenuation relative to the adjacent hepatic parenchyma during the hepatic venous or delayed phase, has been recognised as a strong predictor of HCC [7, 8]. This sign has been included, along with the presence of hypervascularity, in the latest

American Association for the Study of Liver Diseases (AASLD) guidelines for the diagnosis of HCC at multiphasic MDCT, MRI or contrast-enhanced ultrasonography [1]. Although it is well known that tumour enhancement is best visualised during the late hepatic arterial phase [9, 10], there is no consensus regarding the correct timing for the detection of tumour washout at multiphasic MDCT of the liver. Most commonly, the hepatic arterial phase is followed by the hepatic venous phase, acquired 60–70 s after injection of contrast material [9–12]. In addition, a delayed phase, acquired from 2–10 min after contrast material injection, can follow the hepatic venous phase [13–20] or can occur alone after the hepatic arterial phase [21–23]. Regardless of the phase sequence chosen, to the best of our knowledge, no study has yet compared the hepatic venous and delayed phases for the detection of tumour washout in patients with HCC. The purpose of our study was to compare retrospectively the hepatic venous and delayed phases for the detection of tumour washout during multiphasic MDCT of the liver in patients with HCC who underwent liver transplantation.

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Methods and materials

Our institutional review board granted permission for this retrospective cohort study, which was performed in a large referral hospital for hepatobiliary diseases. Informed consent was waived for this study.

Patients

From January 2003 to April 2006, radiology and pathology records were searched for patients with cirrhosis who underwent multiphasic, contrast-enhanced MDCT before liver transplantation. Of 300 patients who met these inclusion criteria, 48 patients (30 men and 18 women; mean age, 57 years; range, 36–66 years) were diagnosed with 139 HCCs on the basis of pathological examination of the explanted liver. 18 of these 48 patients were excluded either because CT examination was performed more than 90 days before liver transplantation ($n=10$) or because the patient underwent radiofrequency or transarterial chemoembolisation before MDCT ($n=8$). The remaining 30 patients (25 men and 5 women; mean age, 55 years; range, 36–64 years) constituted the study cohort. The underlying cause of cirrhosis included hepatitis C ($n=15$), hepatitis B or D ($n=8$), alcohol abuse ($n=3$) or a combination of viral and alcoholic cirrhosis ($n=2$). In the two remaining patients, no reason for the underlying liver disease was identified, leading to a presumed diagnosis of cryptogenic cirrhosis.

CT technique

All examinations were performed with a 16-section (Brilliance, Philips Medical System, Best, the Netherlands) or 64-section (Somatom Sensation 64, Siemens Medical System, Forchheim, Germany) MDCT scanner, using a dedicated liver CT protocol. Helical scan data were acquired using 16 detector rows and a beam collimation of 1.5 mm (16×1.5 mm) or 64×0.6 mm, gantry rotation time of 0.5 or 0.33 s, section reconstruction thickness of 3.0 mm, image reconstruction interval of 3.0 mm, and an effective tube current-time product of 150–250 mAs and 120 kVp. All patients received 2 ml kg^{-1} total body weight of an intravenous (iv), non-ionic contrast medium containing an iodine concentration of 350 mg ml^{-1} (iomeprol, Iomeron 350®; Bracco Imaging, Milan, Italy). Contrast medium was administered via a mechanical power injector (Stellant D CT, Medrad, Pittsburgh, PA) at a rate of $3\text{--}5 \text{ ml s}^{-1}$ through an 18–20-gauge iv catheter inserted into an arm vein, followed by a flush of 40 ml of saline administered at the same injection rate. CT was performed immediately before and after contrast medium administration during the hepatic arterial, hepatic venous and delayed phases. Computer-assisted bolus-tracking software was used to determine the optimal scan delay for the hepatic arterial phase in each patient. Acquisition of the hepatic arterial phase started 12 s after the trigger threshold (120 Hounsfield units (HU)) was reached at the level of the abdominal aorta. The hepatic venous and delayed phases started 55 and 120 s, respectively, after the trigger threshold.

Pathological analysis

In all cases, gross and histological analyses of the explanted liver were performed by an experienced liver pathologist. All explanted livers were fixed in formalin and sectioned at 7–10-mm intervals in the transverse plane. All lesions that differed from the background liver in terms of size, texture or colour were fixed in formalin, embedded in paraffin and further sectioned for additional evaluation. Treated lesions with complete necrosis at histological examination were excluded from analysis. For each analysed lesion, location (Couinaud segment and proximity to well-defined vascular landmarks) and size were recorded by the attending pathologist. Pathology reports were considered the standard of reference for this study.

Qualitative analysis

CT images were assessed by two radiologists, who were blinded to the review process, with 6 and 4 years of experience in hepatobiliary imaging on a Picture Archiving and Communicating System (PACS) monitor (Impax 5.4, Agfa Healthcare, Mortsel, Belgium). Readers were blinded to the patient's history, clinical CT interpretation, histological analysis of the explanted liver and the aim of the study. During two reading sessions, the following two image sets were reviewed separately and independently: (i) unenhanced hepatic arterial phase and hepatic venous phase images and (ii) unenhanced hepatic arterial phase and delayed phase images. To minimise recall bias, the two reading sessions were separated by a 4 week interval. Readers were allowed to adjust window settings (window width and level) according to their own preferences. Disagreement between readers was resolved by consensus. To ensure that both readers assessed the same liver lesion and that only histopathologically confirmed HCCs were evaluated, the study co-ordinator (blinded to the review process, with 10 years of experience in body CT) designated the liver lesions to be analysed on a segmental liver map. This map was distributed to both observers prior to each reading session. Because the purpose of our study was to assess the correct phase for the detection of tumour washout, rather than to determine the accuracy of this sign for the diagnosis of HCC, only those lesions delineated on the map and recognised on the images by the study co-ordinator were included in the analysis. During each reading session, the two observers qualitatively assessed lesion attenuation compared with the adjacent hepatic parenchyma for both image sets. Lesions were categorised as hyper-, iso- or hypoattenuating in comparison with the surrounding hepatic parenchyma. If a lesion exhibited heterogeneous attenuation, its categorisation was based on the attenuation of the dominant component. On the basis of assessment of the hepatic arterial phase images, hyperattenuating tumours were defined as hypervascular HCCs, whereas iso- or hypoattenuating lesions were considered to be hypovascular HCCs. Subjective tumour washout was deemed to be present if an HCC lesion hyper- or isoattenuating to the liver on a hepatic arterial phase image subsequently appeared hypoattenuating compared with the surrounding liver parenchyma on hepatic venous or delayed phase images [12, 18]. In addition, the presence of a perilesional

capsule (defined as a partial or complete hyperattenuating rim around the nodule on a hepatic venous or delayed phase image) was recorded by the readers.

Quantitative analysis

Quantitative analysis was performed by the study coordinator on the same lesions and using the same PACS monitor as was used for the qualitative assessment. For each patient, lesion and liver attenuation (HU) were measured by means of a circular region of interest (ROI) (mean size, 1.1 ± 0.7 cm²; range, 0.4–9 cm²) placed at an identical position on the images from each imaging phase (unenhanced, hepatic arterial, hepatic venous and delayed). For each tumour, the ROI was drawn to encompass as much of the lesion as possible, excluding areas of necrosis or calcification. Liver attenuation was measured as the average value of three different ROIs (1 cm²) drawn on the hepatic parenchyma adjacent to the lesion. Care was taken not to place ROIs over vascular structures, dilated biliary ducts or artefacts.

For each pathologically confirmed HCC lesion, the tumour-to-liver contrast (TLC) was calculated during each of the four imaging phases as the difference in attenuation between the lesion and the surrounding liver parenchyma [24]. Objective washout was deemed present if a tumour with positive TLC during the hepatic arterial phase demonstrated a negative TLC (lesion attenuation lower than that of the adjacent liver parenchyma) on the hepatic venous or delayed phase images [12].

Statistical analysis

The rates of subjective and objective detection of tumour washout on hepatic venous and delayed phase images were compared using the McNemar's test. A separate analysis of subjective washout was conducted for hypervascular HCC nodules. Mean attenuation values of lesions and liver parenchyma were plotted in time-attenuation curves. Correlation between tumour size and the presence of intralesional contrast washout was analysed using the Student's *t*-test. TLC values obtained from the hepatic venous phase and delayed phase images were reported in box-and-whisker plots and the significance of difference of the mean values was assessed using the Student's *t*-test. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using commercially available software (SPSS 16.0.0 for Macintosh; SPSS, Chicago, IL).

Results

Pathological analysis

61 HCC lesions in 30 patients were examined pathologically (mean size, 14 ± 4 mm; range, 4–42 mm). The average number of HCC lesions per patient was 2 ± 1.1 (range, 1–6). The HCC was solitary in 19 patients, but 2 or more HCC nodules were detected in the remaining 11 patients.

Table 1. Number of hepatocellular carcinoma lesions of each appearance by tumour size

Tumour size	Imaging phase														
	Unenhanced						Hepatic arterial			Hepatic venous			Delayed		
	Hypo	Iso	Hyper	Hypo	Iso	Hyper	Hypo	Iso	Hyper	Hypo	Iso	Hyper	Hypo	Iso	Hyper
≤10mm (n=13)	3 (24%)	10 (76%)	0 (0%)	1 (8%)	1 (8%)	11 (84%)	2 (16%)	10 (76%)	1 (8%)	6 (54%)	7 (46%)	0 (0%)			
10–20mm (n=23)	10 (43%)	13 (57%)	0 (0%)	0 (0%)	3 (13%)	20 (87%)	9 (39%)	13 (57%)	1 (4%)	19 (82%)	4 (18%)	0 (0%)			
≥20mm (n=12)	2 (17%)	10 (83%)	0 (0%)	1 (8%)	0 (0%)	11 (92%)	6 (50%)	5 (42%)	1 (8%)	12 (100%)	0 (0%)	0 (0%)			
Total (n=48)	15 (31%)	33 (69%)	0 (0%)	2 (4%)	4 (8%)	42 (88%)	17 (36%)	28 (58%)	3 (6%)	37 (77%)	11 (23%)	0 (0%)			

Hyper, hyperattenuating; hypo, hypoattenuating; iso, isoattenuating.

Qualitative analysis

48 (79%) of 61 HCCs (mean size, 16 ± 8 mm; range, 8–42 mm) in 25 patients were detected at MDCT during at least 1 imaging phase. Of these 48 lesions, 13 HCC nodules were ≤ 10 mm in diameter, 23 were between 10 and 20 mm, and 12 were ≥ 20 mm. The remaining 13 of 61 lesions (21%) (mean size, 9 ± 4 mm; range, 4–15 mm) in 5 patients were not detected at CT by either observer during the 2 reading sessions.

Table 1 summarises tumour attenuation relative to that of the surrounding liver during each imaging phase. Of the 48 HCCs identified at imaging, 42 (88%) were hypervascular and 6 (12%) were hypovascular (4 iso- and 2 hypoattenuating to the surrounding liver parenchyma

on hepatic arterial phase images). For the two hypoattenuating lesions in two patients, washout could not be diagnosed because of lesion hypoattenuation on the hepatic arterial phase images. Of the 46 (96%) hyper- or isoattenuating tumours, subjective washout was present on hepatic venous phase images in 15 (33%) tumours, significantly more, 35 (76%), were seen on delayed phase images ($p < 0.001$). Washout that was detected subjectively on hepatic venous phase images was confirmed on delayed phase images in all cases (Figure 1). For 20 of the 46 tumours (43%) in 9 patients, washout was deemed present only on delayed phase images (Figure 2). In 11 of 46 HCCs (24%) in 5 patients, there was no evidence of subjective washout on both hepatic venous and delayed phase images (Figure 3). These

(a)

(b)

(c)

Figure 1. 51-year-old man with alcohol-induced cirrhosis and a pathologically proven 31 mm hepatocellular carcinoma (HCC) lesion. (a) Axial contrast-enhanced CT scan of the liver obtained during the hepatic arterial phase shows the tumour (arrow) as a heterogeneously enhancing mass in the hepatic dome. (b) Axial contrast-enhanced CT scan of the liver obtained during the hepatic venous phase at the same level as (a) shows the tumour (arrow) as heterogeneously and slightly hypoattenuating (washout) compared with the surrounding liver parenchyma. (c) Axial contrast-enhanced CT scan of the liver obtained during the delayed phase at the same level as (a) and (b) clearly depicts the tumour (arrow) as homogeneously hypoattenuating (visible washout) relative to the surrounding liver parenchyma.

Figure 2. 60-year-old man with hepatitis C cirrhosis and a pathologically proven 20 mm hepatocellular carcinoma (HCC) nodule. (a) Axial contrast-enhanced CT scan of the liver obtained during the hepatic arterial phase shows the tumour as a hyperattenuating nodule (arrow) in the right hepatic lobe. (b) Axial contrast-enhanced CT scan of the liver obtained during the hepatic venous phase at the same level as (a). The tumour is isoattenuating to the surrounding hepatic parenchyma and is not visible. (c) Axial contrast-enhanced CT scan of the liver obtained during the delayed phase at the same level as (a) and (b) demonstrates the tumour as a slightly hypoattenuating area (visible washout) (arrow) compared with the surrounding hepatic parenchyma.

tumours were significantly smaller (mean size, 10.5 ± 2 mm) than the 35 HCC nodules exhibiting a washout sign (mean size, 18.5 ± 9 mm) ($p=0.001$).

The patterns of enhancement of hyper- and hypovascular HCCs are summarised in Table 2. Among the 42 hypervascular HCCs, subjective washout was deemed present in 12

(29%) and in 31 (74%) lesions on hepatic venous and delayed phase images, respectively ($p<0.001$).

A peripheral tumour capsule was identified in 8 (17%) of 48 HCC nodules. The capsule was seen during the hepatic venous phase in two lesions and during the delayed phase in all eight lesions.

(a)

(b)

(c)

Figure 3. 54-year-old woman with hepatitis C cirrhosis and a pathologically proven 11 mm hepatocellular carcinoma (HCC) lesion. (a) Axial contrast-enhanced CT scan of the liver obtained during the hepatic arterial phase shows a homogeneously hyperattenuating tumour (arrow) bulging from the right hepatic lobe surface. (b) Axial contrast-enhanced CT scan of the liver obtained during the hepatic venous phase at the same level as (a) shows the tumour (arrow) as slightly hyperattenuating to the surrounding hepatic parenchyma. (c) Axial contrast-enhanced CT scan of the liver obtained during the delayed phase at the same level as (a) and (b). The tumour is isoattenuating to the surrounding hepatic parenchyma and washout is not visible.

Quantitative analysis

Table 3 reports mean tumour and liver attenuation values and mean TLC values for each imaging phase. The mean tumour attenuation value was 102.7 ± 20.1 HU on

hepatic arterial phase images and 104.7 ± 14.4 HU on hepatic venous phase images, decreasing to 95.8 ± 16.2 HU on delayed phase images. The mean attenuation measurement for the hepatic parenchyma was greatest during the hepatic venous phase (115.4 ± 12.3 HU),

Table 2. Patterns of enhancement in hepatocellular carcinoma (n=48)

Hepatic arterial phase	Hepatic venous phase	Delayed phase	n (%)
Hyperattenuating	Hypoattenuating	Hypoattenuating	12 (25)
Hyperattenuating	Iso- or hypoattenuating	Hypoattenuating	19 (40)
Hyperattenuating	Iso- or hypoattenuating	Isoattenuating	11 (23)
Isoattenuating	Isoattenuating	Hypoattenuating	3 (6)
Isoattenuating	Hypoattenuating	Hypoattenuating	1 (2)
Hypoattenuating	Hypoattenuating	Hypoattenuating	2 (4)

Hyperattenuating tumours on hepatic arterial phase images were considered to be hypervascular hepatocellular carcinomas (HCCs). Iso- and hypoattenuating tumours on hepatic arterial phase images were considered to be hypovascular HCCs.

decreasing to 111.7 ± 12.5 HU during the delayed phase. Mean attenuation values of the liver parenchyma and HCCs are plotted in a time-attenuation curve in Figure 4. Of the 48 total lesions, 46 (96%) presented positive TLC during the hepatic arterial phase. Of these 46 lesions, objective washout was present in 30 (65%) HCC nodules during the hepatic venous phase and in 42 (91%) during the delayed phase ($p=0.001$). The delayed phase images yielded significantly higher mean TLC absolute values than the hepatic venous phase images (-16.1 ± 10.8 HU vs -10.5 ± 10.2 HU; $p<0.001$) (Figure 5).

Discussion

Our results demonstrate that the delayed phase is superior to the hepatic venous phase for the detection of the washout sign of HCC at multiphasic MDCT of the liver. Both subjective and objective washout was more frequently depicted on the delayed phase images (76% and 91%, respectively) than on the hepatic venous phase images (33% and 65%, respectively) ($p<0.001$ and $p=0.001$, respectively). The fact that the washout sign was detected more frequently by subjective rather than objective examinations may be related to the limited ability of the observers to perceive qualitatively minimal change in attenuation between the tumour and the surrounding liver parenchyma. These findings were reflected in our TLC results, which showed significantly higher TLC absolute values during the delayed phase (-16.1 ± 10.8 HU) than during the hepatic venous phase (-10.5 ± 10.2 HU) ($p<0.001$), a finding consistent with greater conspicuity of tumour washout during the delayed phase.

Our findings may be partly explained by the analysis of the progression of tumour and liver attenuation over the different imaging phases. In our series, both liver parenchyma and HCC reached their maximum enhancement during the hepatic venous phase. Previous authors have suggested that this finding is a consequence of the intralesional persistence of the contrast medium during the arterial phase [15, 25]. The cause of tumour washout

remains poorly understood, but according to the prevailing theory, this sign is a reflection of decreased intranodular portal blood supply [25, 26]. Therefore, it may be postulated that, compared with the hepatic venous phase, the longer interval associated with delayed phase results in more accentuated drainage of contrast material from the tumour, thus explaining the higher prevalence of tumour washout during the later delayed phase [14, 16].

The percentage of HCCs showing washout in our series is lower than that previously reported for either the hepatic venous phase (58–86%) [12, 15, 19] or the delayed phase (80–85%) [13–15, 21]. Several reasons may explain this discrepancy. First, our study systematically compared hepatic venous and delayed phase images for the detection of washout within the same tumour. Second, the pathological correlation with the explanted liver in our study was not seen in the majority of the previous studies [12–15, 21]. Third, there was an extremely wide variation in the scan delay (2–10 min) before the acquisition of delayed phase images in previous studies [12–15, 19]. And fourth, the tumours in our series were small (mean, 16 ± 8 mm). In contrast to the results reported previously by Lee et al [12], in our study, the tumours that did not show washout during either the hepatic venous or delayed phase ($n=11$) were significantly smaller (mean size, 10.5 ± 2 mm) than those that did exhibit washout (mean size, 18.5 ± 9 mm) ($p=0.001$). The lack of correlation between size and washout in Lee's study could be explained by the large mean size (75 mm) of the lesions analysed. In many transplant centres that have adopted the Model for End-Stage Liver Disease–HCC scoring system, the presence of tumour as defined by the Milan criteria significantly increases the priority of cirrhotic patients on the liver transplantation waiting list [27]. In our hospital, the assessment of cirrhotic patients before liver transplantation is conducted with either MDCT or MRI; because of scanner availability, the majority of patients are evaluated by MDCT. According to the latest AASLD guidelines, a non-invasive diagnosis of HCC at contrast-enhanced MDCT requires that both the presence of nodule hypervascularity and venous washout are demonstrated

Table 3. Hepatocellular carcinoma (HCC) and liver parenchyma mean ($\pm$ standard deviation) attenuation values (HU) and tumour-to-liver contrast (TLC) by imaging phase

	UE	HAP	HVP	DP
HCC	52.8 ± 8.5	102.7 ± 20.1	104.7 ± 14.4	95.8 ± 16.2
Liver parenchyma	52.9 ± 9.4	78.0 ± 14.6	115.4 ± 12.3	111.7 ± 12.5
TLC	0.1 ± 0.1	24.7 ± 12.1	-10.5 ± 10.2	-16.1 ± 10.8

DP, delayed phase; HAP, hepatic arterial phase; HVP, hepatic venous phase; UE, unenhanced.

Figure 4. Time-attenuation curve of hepatocellular carcinomas (dashed line) and liver parenchyma (continuous line). DP, delayed phase; HAP, hepatic arterial phase; HVP, hepatic venous phase; UE, unenhanced.

[1]. Among the hypervascular lesions in our series ($n=42$), the percentage of tumours showing washout significantly increased from 29% on hepatic venous phase images to 74% on delayed phase images ($p<0.001$). In addition, the delayed phase was superior to the hepatic venous phase for the demonstration of tumour capsule (seen in eight lesions during the delayed phase and in only two lesions during the hepatic venous phase) in accordance to previous observations [15, 28]. On the basis of these two findings, we recommend that the acquisition of the delayed phase be included in MDCT study protocols for cirrhotic patients. Although the scan delay used for the acquisition of this phase is extremely variable, a scan delay of 120 s after the start of contrast material injection

Figure 5. Box-and-whisker plot shows median (middle line of each box), quartiles (top and bottom line of each box) and upper and lower adjacent (upper and lower whiskers for each box) tumour-to-liver contrast (TLC) values (HU) for the hepatic venous and delayed phases. Mean TLC values measured on the delayed phase images (-16.1 ± 10.8 HU) were significantly greater than those measured on the hepatic venous phase images (-10.5 ± 10.2 HU) ($p<0.001$).

has recently been shown to minimise the risk of showing hypervascular HCCs as isoattenuating relative to the surrounding liver parenchyma [29]. Other authors [18] acquire the delayed phase 180 s after the start of bolus injection and have found this delay to be effective in demonstrating HCC washout. Nevertheless, we are not aware of any study comparing 120 s delayed phase images with 180 s delayed phase images in this setting. It should be noted that the inclusion of multiple phases in any CT study of cirrhotic patients continues to cause concern owing to increased radiation exposure and tube loading [30, 31]. In our series, no washout that was visible in the hepatic venous phase was missed in the delayed phase, but we did not provide enough evidence to suggest the elimination of the hepatic venous phase. Further studies are needed to prove the reliability of delayed phase images for the identification of findings usually assessed on hepatic venous phase images, such as portal vein thrombosis, porto-systemic vascular shunts and other abdominal parenchymal organs [16].

The AASLD guidelines for the diagnosis of HCC are equivocal as regards the interpretation of hypovascular nodules [32]. In our population, 6 of the 48 HCCs (12%) were hypovascular. For these tumours, the delayed phase images performed slightly better than the hepatic venous phase images in demonstrating tumour hypoattenuation, in accordance with previous investigations [14, 16, 17]. These tumours cannot be correctly characterised by means of contrast-enhanced MDCT following the current guidelines because their enhancement is similar, or inferior, to that of the surrounding liver parenchyma on the hepatic arterial phase images. At the same time, the detection of tumour washout is based on the relative attenuation of the lesion and the adjacent hepatic parenchyma, and so this sign cannot be assessed for lesions that are hypoattenuating on hepatic arterial phase images. A possible solution to allow for the inclusion of these lesions would be to define washout as a decrease in attenuation within the lesion itself between the arterial phase and the hepatic venous or delayed phase, rather than a decrease relative to the adjacent liver parenchyma.

Besides its retrospective nature, four potential limitations of our study merit consideration. First, our data were obtained from a small patient population ($n=30$) and thus need to be prospectively validated on a larger sample size. At the same time, we selected only patients with cirrhosis and pathologically proven HCC at liver transplantation. Although this approach reduced the number of eligible patients, it enabled us to investigate the presence of washout across the entire range of lesion size, which would have been challenging, and potentially inaccurate, if we had used either biopsy or imaging follow-up as alternative reference tests, particularly for smaller lesions (<2 cm). Second, HCC grading was not included in our analysis because this information was not available in the retrospective review of the pathological reports. This is particularly important because the results reported in the literature conflict with regard to the correlation between HCC histological grading and lesion washout on contrast-enhanced cross-sectional imaging examinations [12, 33]. Third, in our study, readers were asked to assess only pathologically proven HCCs and no information was collected regarding other lesions that might have been present, such as dysplastic nodules. The purpose of this

study was to assess the correct phase for the detection of tumour washout, rather than to determine the accuracy of this sign for the diagnosis of HCC. Moreover, the retrospective design is not optimal for an accuracy study because lesions such as dysplastic nodules might not be routinely described in pathology reports. Fourth, we used 12 s after the trigger threshold for the acquisition of the hepatic arterial phase, whereas Sultana et al [34] have recently demonstrated that 18–20 s is the optimal delay for the detection of hypervascular HCC in cirrhotic livers. Our study was conducted before the publication of these data. The shorter delay could have influenced the enhancement pattern of the detected HCCs.

Conclusion

The results of our study demonstrate that, compared with the hepatic venous phase, the delayed phase yields a significantly higher detection rate of tumour washout during multiphasic MDCT in patients with cirrhosis and pathologically proven HCC.

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