

7-1-2010

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Chaodumrong, R; Tanpowpong, N; and Vachiranubhap, B. (2010) "Hepatocellular carcinoma in cirrhotic liver: CT findings and the usefulness of delayed phase scan," *Chulalongkorn Medical Journal*: Vol. 54: Iss. 4, Article 5.

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Hepatocellular carcinoma in cirrhotic liver: CT findings and the usefulness of delayed phase scan

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Chaodumrong R, Tanpowpong N, Vachiranubhap B. Hepatocellular carcinoma in cirrhotic liver: CT findings and the usefulness of delayed phase scan. Chula Med J 2010 Jul - Aug; 54(4): 347 - 61

- Background** : *Most hepatocellular carcinomas (HCCs) occur in an underlying cirrhotic liver. Some of which are difficult to diagnose because they do not show typical enhancement pattern, and cirrhotic nodules can mimic an HCC. Although multiphasic dynamic computed tomography (CT) has been used for detecting HCC, the usefulness of delayed phase scan is unclear.*
- Objectives** : *To analyze CT appearances of HCCs and other associated findings in cirrhotic livers, and to determine the usefulness of delayed phase scan for detecting HCCs.*
- Setting** : *Department of Radiology, Faculty of Medicine, Chulalongkorn University*
- Research design** : *Retrospective study*
- Materials and Methods** : *Fifty-three cirrhotic patients with 109 hepatic lesions underwent multiphasic dynamic CT scan. They were considered to have HCCs according to the Barcelona EASL 2000 HCC guideline and AASLD criteria. The combination of unenhanced, arterial and portal venous phase scans and the combination of*

unenhanced, arterial, portal venous and delayed phase scans of each patient was reviewed separately by two independent radiologists. Each lesion was evaluated regarding its size, focalization, location, attenuation, enhancement pattern and confidence level for diagnosing HCC.

Results : *Most HCCs showed wash out of contrast material on portal venous phase scan (64.2 -66%). Approximately, one-fourth of HCCs showed wash out on delayed phase scan, higher percentage in small HCCs with a diameter of less than 2 cm (31.6 - 42.1%) compared to those with a diameter of more than 2 cm (23.4 - 24.5%). On delayed phase scan, 40.4% of HCCs showed capsular enhancement. There were tumor involvement of portal veins and hepatic veins in 17 patients (32.1%) and one patient (1.9%), respectively. Arterioportal shunt was present in 5 patients (9.4%) and bile duct dilatation was found in 3 patients (5.7%). Mean confidence level for diagnosing HCC by combined unenhanced, arterial and portal venous phase scans was 4.28-4.45 and 4.63 for combined unenhanced, arterial, portal venous and delayed phase scans. The confidence level increased significantly after adding the delayed phase scan ($P<.05$).*

Conclusion : *CT findings on delayed phase scan are helpful in the diagnosis of HCC, especially in small HCCs with a diameter of less than 2 cm. Adding the delayed phase scan shows significantly increased confidence level and can confirm the diagnosis.*

Keywords : *Hepatocellular carcinoma, delayed phase scan, computed tomography.*

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Received for publication. January 25, 2010.

รวมพอ เขาว์ดำรงค์, ญัฐพร ตันเฝ้าพงษ์, บุษกร วชิรานุภาพ. มะเร็งตับในภาวะตับแข็ง:
ลักษณะทางเอกซเรย์คอมพิวเตอร์และประโยชน์ของดีเลย์เฟสแกน. *จุฬาลงกรณ์เวชสาร* 2553
ก.ค. - ส.ค.; 54(4): 347 - 61

- เหตุผลของการทำวิจัย** : มะเร็งตับส่วนใหญ่มักพบในผู้ป่วยที่มีภาวะตับแข็ง ในกลุ่มนี้บางส่วนจะวินิจฉัยได้ยาก เนื่องจากไม่ได้แสดงลักษณะที่เป็นสัญลักษณ์ของมะเร็งตับ และมีปุ่มเนื้อที่เกิดในภาวะตับแข็ง ซึ่งให้ลักษณะคล้ายมะเร็งตับ แม้ว่าการตรวจหามะเร็งตับโดยเอกซเรย์คอมพิวเตอร์ที่มีการฉีดสารทึบรังสีและสแกนแบบมัลติเฟสถูกนำมาใช้แล้วหลายปี แต่ประโยชน์ของดีเลย์เฟสยังไม่ชัดเจน
- วัตถุประสงค์** : เพื่อวิเคราะห์ลักษณะทางเอกซเรย์คอมพิวเตอร์ของมะเร็งตับในผู้ป่วยที่มีภาวะตับแข็ง และศึกษาประโยชน์ของดีเลย์เฟสสแกนในการตรวจหามะเร็งตับ
- สถานที่ทำการศึกษา** : ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- รูปแบบการวิจัย** : การวิจัยย้อนหลัง
- ตัวอย่างและวิธีการศึกษา** : ผู้ป่วย 53 คน ซึ่งได้รับการตรวจด้วยเอกซเรย์คอมพิวเตอร์แบบมัลติเฟส พบ 109 รอยโรคในตับ และได้รับการวินิจฉัยว่าเป็นมะเร็งตับตาม Barcelona EASL 2000 HCC guideline และ AASLD criteria ภาพที่ได้จากการตรวจเอกซเรย์คอมพิวเตอร์ในผู้ป่วยแต่ละคนถูกแบ่งออกเป็นสองชุด คือ แบบที่ไม่มีและแบบที่มีดีเลย์เฟสสแกน รังสีแพทย์ 2 ท่านวิเคราะห์หรือโรคในภาพแต่ละชุดโดยคำนึงถึงขนาดจำนวนตำแหน่ง attenuation enhancement pattern และระดับความมั่นใจในการวินิจฉัยมะเร็งตับ
- ผลการศึกษา** : มะเร็งตับส่วนใหญ่ (64.2 - 66%) จะแสดงลักษณะ wash out ใน portal venous เฟสสแกน ซึ่งเป็นสัญลักษณ์ของมะเร็งตับ ประมาณหนึ่งในสี่ของรอยโรคมีลักษณะ wash out ในดีเลย์เฟสและมีสัดส่วนสูงในกลุ่มมะเร็งตับขนาดเล็กกว่า 2 ซม. (31.6 - 42.1%) เมื่อเปรียบเทียบกับมะเร็งตับที่มีขนาดมากกว่า 2 ซม. (23.4 - 24.5%) 40.4% ของมะเร็งตับแสดง capsular enhancement ในดีเลย์เฟสสแกน พบภาวะก้อนมะเร็งลูก้าหลอดเลือดดำportal และ หลอดเลือดดำ hepatic ในผู้ป่วย 17 ราย (32.1%) และหนึ่งราย (1.9%) ตามลำดับ มี

arterioportal shunt ในผู้ป่วย 5 ราย (9.4%) และพบการขยายออกของ
ท่อน้ำดีในผู้ป่วย 3 ราย (5.7%) ระดับความมั่นใจในการวินิจฉัย
มะเร็งตับเมื่อไม่มีดีเลย์เฟสสแกนเป็น 4.28 - 4.45 และเพิ่มขึ้นอย่างมี
นัยสำคัญเป็น 4.63 เมื่อมีดีเลย์เฟสสแกน ($P < .05$)

สรุป : ผลของเอกซเรย์คอมพิวเตอร์ในดีเลย์เฟสสแกนช่วยในการวินิจฉัย
โรคมะเร็งตับ โดยเฉพาะก้อนมะเร็งที่ขนาดเล็กกว่า 2 ซม.

คำสำคัญ : มะเร็งตับ, ดีเลย์เฟสสแกน, เอกซเรย์คอมพิวเตอร์

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, with high incidences in Africa, East and Southeast Asia.⁽¹⁻⁴⁾ Most HCCs are found associated with underlying liver cirrhosis and chronic hepatitis.^(1,5) As HCCs typically receive primary blood supply from the hepatic artery and have decreased portal venous blood supply, they show arterial enhancement and wash out on portal venous phase. Nevertheless, some small or well-differentiated HCCs may not have prominent hepatic arterial supply and show no enhancement on arterial phase.⁽⁶⁻⁹⁾ Furthermore, cirrhotic nodules can mimic a hepatic tumor which is more difficult to distinguish from HCC.^(10, 11)

Currently, multiphasic dynamic computed tomography (CT) has become an important tool in characterizing hepatic tumors, screening of high risk patients for HCCs and follow-up imaging of patients after treatment of a hepatic tumor. The dynamic CT with arterial and portal venous phases has been shown to have a high detection rate of HCC, and therefore is widely used. In the role of additional acquisition, delayed phase scan is still controversial. Hwang *et al.*⁽¹²⁾ described that although delayed phase more easily showed wash out pattern than with portal venous phase, there was no statistical significance of detectability of nodular HCC. The data also was supported by the study of Choi *et al.*⁽¹³⁾ which determined no significant difference in the detection of HCCs between the dual phase and triple phase CT scans. So, identifying the value of adding delayed phase is important because the more acquisition, the more radiation exposure to the patient.

We therefore studied CT appearances of HCCs and the associated findings in cirrhotic liver

and the usefulness of the delayed phase scan in detecting HCCs.

Materials and Methods

Subjects

We retrospectively reviewed CT imaging of cirrhotic patients who had at least one hepatic lesion and underwent unenhanced and triple phase dynamic CT study at our institute between September 2005 and December 2008. The patients who had previously undergone transarterial chemoembolization (TACE) or portal vein embolization (PVE) before CT were excluded because it may obscure lesions, interfere with interpretation and cause imaging bias. There were 109 cirrhotic patients included in our study. Of the 109 patients, 53 patients (38 men, 15 women; age range 34 -86 years; mean age, 60.43 years old) with 109 lesions were considered to have HCCs according to the Barcelona EASL 2000 HCC guideline and AASLD criteria^(14,15); pathological confirmation of any size tumor in 16 (30.2%) patients, diagnosis by 2 coincident imaging techniques of lesions more than 2 cm in 9 (17%) patients; and diagnosis by one imaging technique and a level of alpha-fetoprotein (AFP) over 200 ng/ml in lesions more than 2 cm in 28 (52.8%) patients (Fig. 1).

Approval of this study was obtained from the Institutional Review Board without requirement of informed consent for retrospective review of patients' record and images.

CT techniques

All patients underwent unenhanced and triple-phase helical CT scan (hepatic arterial, portal venous and delayed phase scans) during one breath hold.

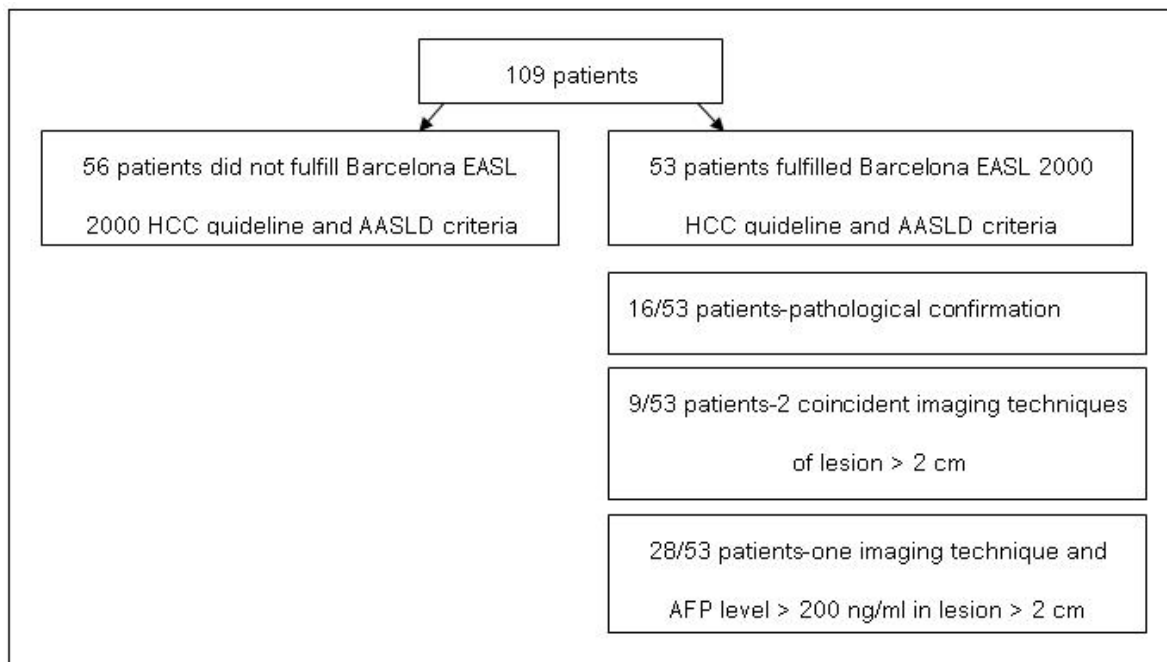


Figure 1. Flow chart demonstrates presence of HCC according to the Barcelona EASL 2000 HCC guideline and AASLD criteria

A multi-detector row helical scanner (Somatom Sensation plus 16, Siemens Medical Solution, Germany) was used with the following parameters: 16 x 1.5 mm collimator, 1 pitch and 0.5 sec rotation time. A dynamic CT scan was performed using a bolus tracking technique. The hepatic arterial and portal venous phases were obtained at 30 - 35 seconds and 65-70 seconds, respectively after the start of the injection of 100 ml of contrast material using iopromide (Ultravist®) or iobitridol (Xenetix®). The delayed phase was performed at 5 minutes. The contrast material was injected by an automatic injector at 3 - 4 ml/sec depending on ability of the patients' peripheral veins. All images were sent to the picture archiving and communication system (PACS).

Image analysis

Two radiologists (N.T. and B.V. with 2 and 4

years of experience in abdominal imaging) separately and individually analyzed the CT findings. They knew that the patients had liver cirrhosis but they were given no other information about the patients, except for their age and gender. Two different readings were performed for each patient in the following order: the combination of unenhanced, arterial and portal venous phase images and the combination of unenhanced, arterial, portal venous and delayed phase images. The window level of each image was adjusted individually. The interval between reading sessions was about 4 weeks to minimize learning bias.

The hepatic nodule or mass was characterized with respect to size, focalization, location, attenuation and enhancement pattern of the tumor. The presence of portal or hepatic veins involvement, bile duct dilatation, portal hypertension or arteriportal shunting was also mentioned. Capsular

enhancement of the tumor in delayed phase was identified. Arterial enhancement of the tumor was identified by an increase in attenuation of 15 - 20 HU more than adjacent liver parenchyma on hepatic arterial phase. The enhancement pattern of the HCC lesions were classified into 4 categories: lesions that exhibited wash out of contrast material on portal venous phase (hyperdensity on arterial phase, and hypodensity on portal venous and delayed phases); lesions that exhibited wash out of contrast material on delayed phase (hyperdensity on arterial phase, hyperdensity or isodensity on portal venous phase and hypodensity on delayed phase); lesions characterized with no wash out (hyperdensity or isodensity on portal venous and delayed phases); and lesions characterized with no arterial enhancement (hypodensity or isodensity on arterial phase). Small HCCs were defined as those with a tumor size of less than 2 cm.

The readers assigned a confidence level for diagnosis. Each lesion was subjectively scored on a five-point scale as follows: 0, HCC absent; 1, HCC probably absent; 2, HCC possibly present; 3, HCC probably present; and, 4, HCC definitely present.

Confidence scores of 2 or higher were regarded as the presence of HCC. The higher the rating is assigned, the more is the confidence in the diagnosis of HCC. Lesions assigned confidence scores of 0 or 1 were considered as a negative diagnosis.

Statistic analysis

As for the evaluation of interobserver reliability of image interpretation in each phase of CT scan, we used kappa values. Evaluation for rating confidence

level, weighted kappa value (Medcalc program) was applied to measure agreement in the rating of the confidence level for diagnosis of HCC. A value of weighted kappa of less than 0.20 indicated poor agreement; a value of 0.21 - 0.40 indicated fair agreement; a value of 0.41 - 0.60 indicated moderate agreement; a value of 0.61 - 0.80 indicated good agreement; and, a value of 0.81 - 1.00 indicated very good agreement.

Wilcoxon sign rank test was used to establish statistical analysis of the confidence diagnostic level of the two observers in comparison with the level for the dual phase and the triple phase of CT scans. The level of significance was set at a P value < .05.

Cases which did not fulfill all criteria were regarded as HCC by the Barcelona EASL 2000 HCC guideline and AASLD criteria,^(14,15) it did not mean that there are truly no HCC lesions. Therefore, they were not considered as absent for HCC, i.e., their sensitivity and specificity were not able to be determined.

Results

As for the two observers, the kappa value showed very good agreement in interpretation of arterial phase (K = 0.854). There was good agreement in image interpretation in unenhanced phase (K = 0.649), portal venous phase (K = 0.6653) and also in delayed phase (K = 0.647). Weighted kappa value showed good agreement in the rating confidence level (Kw = 0.715).

As for all the 109 tumors, the number of tumors with a diameter of more than 2 cm had 90 lesions. The number of tumors with less than 2 cm in diameter, which were classified as small HCCs, was 19 lesions.

All tumors were detected in both dual-phase and triple-phase CT scans. The confidence level in diagnosis of HCC of each tumor was documented in both the reading of dual and triple phase studies. Mean and P values of confidence level in dual-phase and triple-phase studies determined by the observers are shown in Table 1. The results of means and statistical analysis of the two observers were similar. The mean value of confidence level for diagnosing HCC by dual phase scan and triple phase scan of observer 1 were 4.28 and 4.63, respectively; and, observer 2 were 4.45 and 4.63, respectively. The

confidence level was increased significantly in the triple-phase study.

CT findings of HCCs were characterized into 4 patterns as follows; lesions that wash out on portal venous phase (figure 2); wash out on delayed phase (figure 3); no wash out on portal venous and delayed phases (figure 4); no arterial enhancement (figure 5). All nodules were also categorized into 2 groups bases on their size. Information for enhancement pattern of the tumors and correlation with tumor size are presented in Table 2.

Table 1. Results of statistical analysis of confidence level for diagnosis of HCC.

	Observer 1	Observer 2
Mean		
- Dual phase	4.28	4.45
- Triple phase	4.63	4.63
P value	< 0.001	0.007

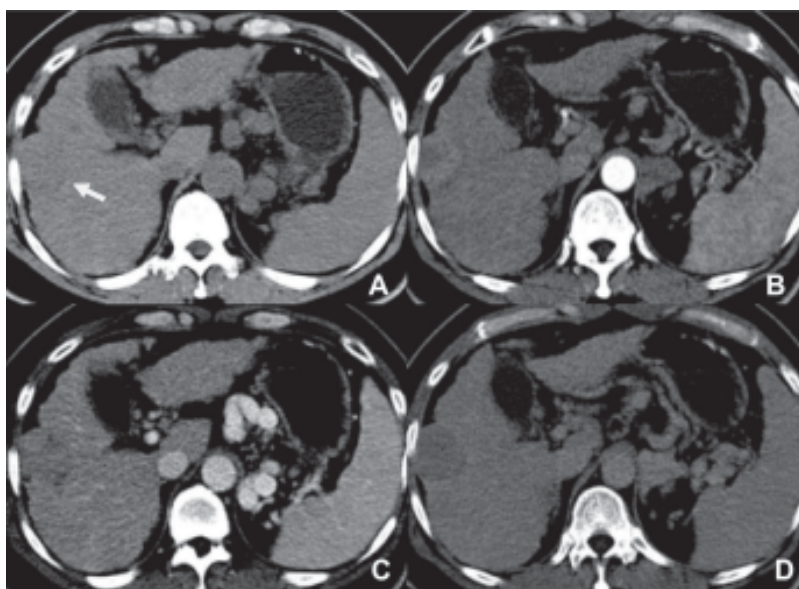


Figure 2. Examples of HCC with wash out on portal venous phase scan in a 52- year-old male with cirrhosis. Unenhanced CT image (A) reveals a hypodensity mass in the right hepatic lobe (arrow). The mass shows inhomogeneous enhancement on arterial phase (B), wash-out on portal venous phase (C) and still hypodensity on delayed phase CT scan (D). This mass was diagnosed to be HCC by criteria of 2 co-incident imaging techniques. Evidence of portal hypertension and collateral circulation is present.

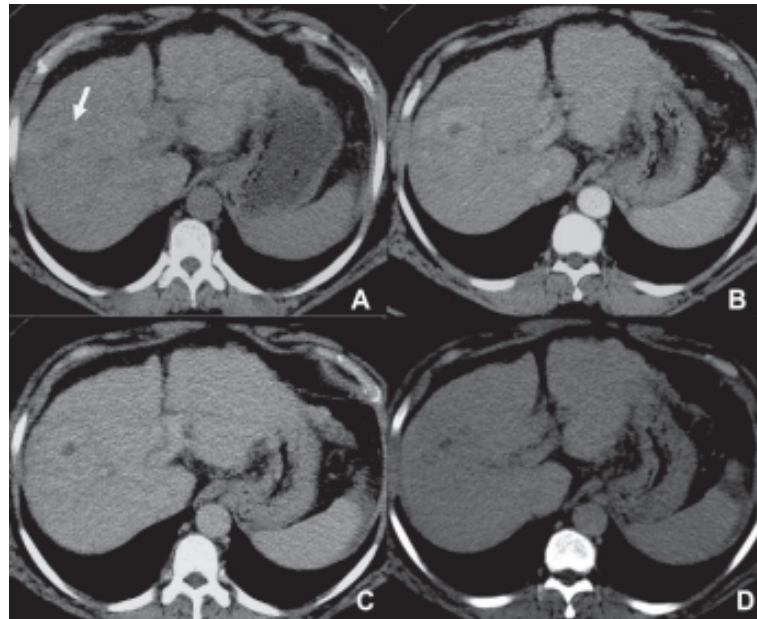


Figure 3. Examples of HCC with wash out pattern on delayed phase scan in a 53-year-old male with cirrhosis. On the unenhanced CT image (A), there is an isodensity lesion with central hypodensity in segment V (arrow). The nodule is hyperdensity on arterial phase (B) and portal venous phase (C) scans. The central region remains hypodensity. On delayed phase scan (D), the nodule becomes hypodensity. The nodule was proved by biopsy to be well-differentiated HCC.

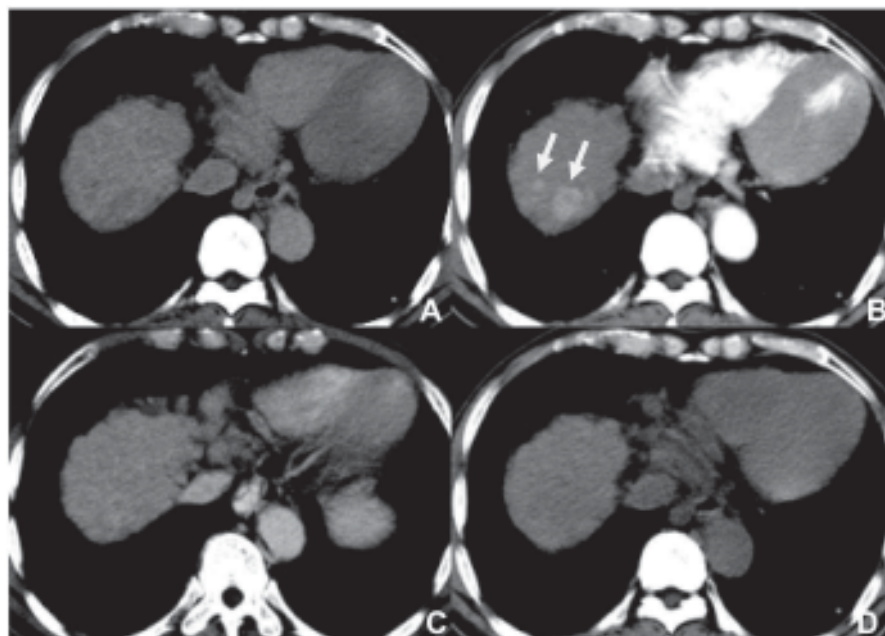


Figure 4. Examples of HCC with no wash out pattern on portal venous and delayed phases in a 63-year-old male with cirrhosis. There are two hypodensity lesions on unenhanced phase (A). The lesions show marked enhancement on arterial phase CT scan (arrows). On portal venous (C) and delayed phase (D) CT scan, they become isodensity as compared with the adjacent normal liver parenchyma.



Figure 5. Examples of HCC with no arterial enhancement pattern. Multiphase CT scan of a 56 year-old male reveals a mass in the right hepatic lobe. The mass is hypodensity on unenhanced phase (A), and demonstrates no enhancement on arterial (B) and portal venous phase (C). Delayed capsular enhancement (arrow) is seen in some part of the lesion (D). On coronal reformat arterial phase CT image (E), there is also no evidence of arterial enhancement. This lesion was biopsied and HCC was reported.

With delayed phase scan, 44 (40.4%) of 109 HCCs revealed capsular enhancement. Of the 44 tumors, there were 6 (13.6%) small HCCs and 38 (86.4%) large HCCs. Examples of delayed capsule enhancement are shown in figure 6. Examples of delayed capsular enhancement were showed in figure 6.

Of the 53 patients, tumor involvement of any branch of the portal veins and hepatic veins were detected in 17 cases (32.1%) and 1 cases (1.9%),

respectively. Arterioportal shunt was presented in 5 cases (9.4%). Example of vascular invasion was demonstrated in figure 7. Bile duct dilatation was found in 3 cases (5.7%). Bile duct was compressed by large tumor in 2 cases, causing proximal bile duct dilatation (figure 8A). In another case, mild dilatation of bile duct was occurred distal to the tumor (figure 8B). There was no evidence of bile duct invasion by the tumor.

Table 2. Enhancement pattern of all tumors and correlation with tumor size.

Enhancement pattern	Observer 1	Observer 2
All tumors		
- Wash-out in portal venous phase	72 (66.0)	70 (64.2)
- Wash-out in delayed phase	28 (25.7)	29 (26.6)
- No wash-out	6 (5.5)	6 (5.5)
- No arterial enhancement	3 (2.8)	4 (3.7)
Size < 2 cm (n = 19)		
- Wash-out in portal venous phase	8 (42.1)	6 (31.6)
- Wash-out in delayed phase	6 (31.6)	8 (42.1)
- No wash-out	3 (15.8)	3 (15.8)
- No arterial enhancement	2 (10.5)	2 (10.5)
Size > 2 cm (n = 90)		
- Wash-out in portal venous phase	64 (71.1)	64 (71.1)
- Wash-out in delayed phase	22 (24.5)	21 (23.4)
- No wash-out	3 (3.3)	3 (3.3)
- No arterial enhancement	1 (1.1)	2 (2.2)

Data are numbers of HCC lesions, and data in parentheses are percentages

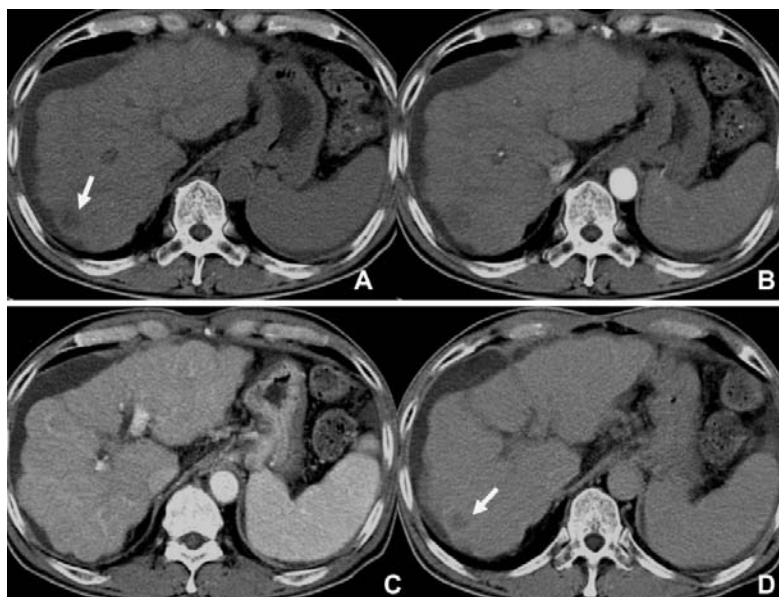


Figure 6. Examples of capsular enhancement of HCC on delayed phase scan in a 69- year-old male. On unenhanced phase scan (A) there is a hypodense nodule in segment VII (arrow). The nodule shows no arterial enhancement on hepatic arterial phase scan (B). On portal venous phase scan (C), the nodule is isodensity to adjacent liver parenchyma. On delayed phase scan (D), the nodule becomes hypodensity with capsular enhancement (arrow). The nodule was proved by biopsy to be poorly-differentiated HCC.

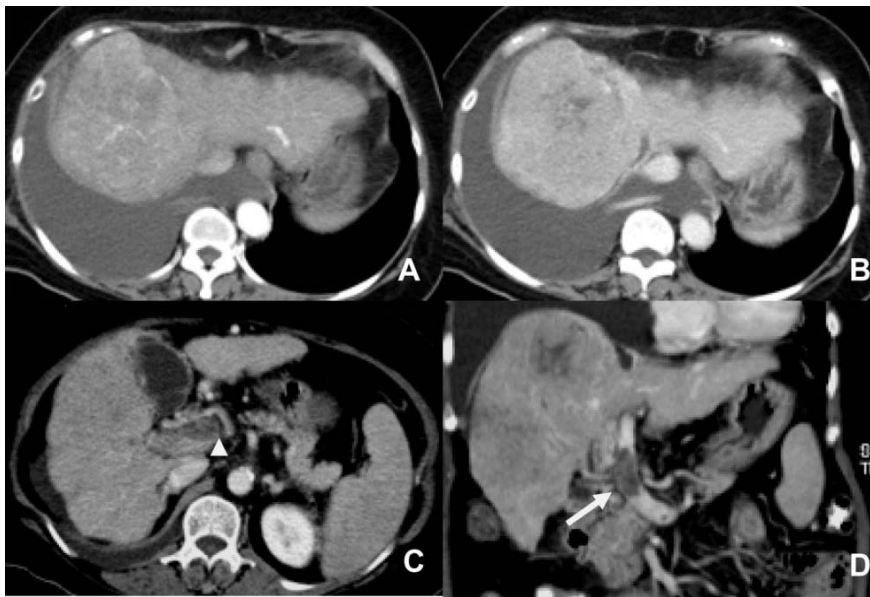


Figure 7. Vascular invasion of HCC. A 63 year-old female underwent multiphasic CT scan. There is a large hypervascular mass in the right hepatic lobe. The mass shows arterial enhancement (A) and wash-out in portal venous phase (B). In the lower topographic level (C), there is a thrombus in the main portal vein (arrowhead). Coronal reformat image of portal venous phase CT scan (D) well shows the thrombus in the main portal vein (arrow).

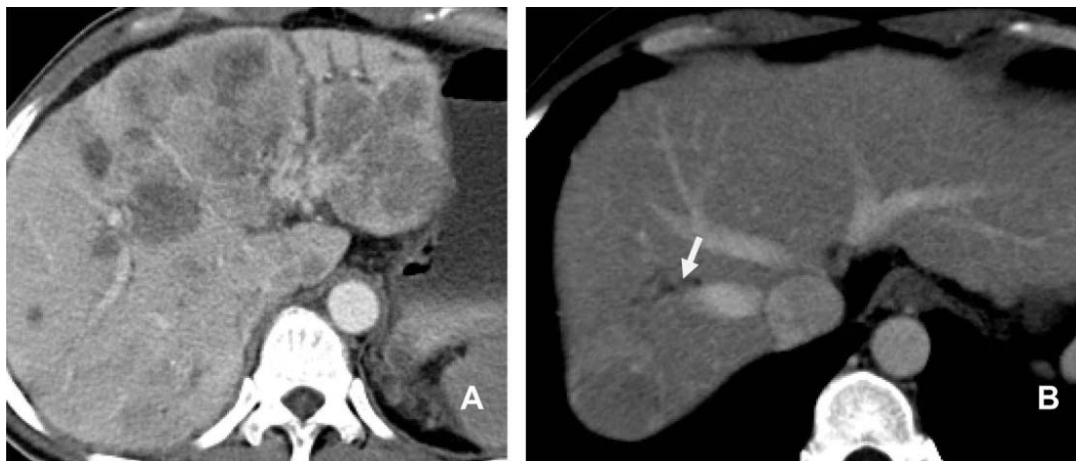


Figure 8. Examples of bile duct dilatation. Figure A shows multifocal hepatic masses in a 56-year-old male. The largest mass compresses the left intrahepatic bile duct, resulting in proximal duct dilatation. Figure B (another patient) shows a mass in the right hepatic lobe and focal intrahepatic bile duct dilatation distal to the mass without evidence of bile duct invasion or cause of obstruction (arrow).

Discussion

Multiphasic dynamic CT scan is widely used for screening HCC in high risk patients such as those with cirrhosis and chronic hepatitis. Detection of HCC with a high degree of accuracy is important because of the diagnosed number, location and vascular involvement of HCC is a prominent factor determining the treatment. As cirrhosis contain various types of nodules, depicting HCC in a cirrhotic liver may be difficult. Therefore, many studies have evaluated the suitable protocol for making the best differentiation of HCC from other benign hepatic nodules.^(16,17)

The usefulness of delayed phase has been investigated in many studies, even though, some researchers published no significant difference in the combination of the arterial and portal venous phases, so-called the dual phase scan and the triple phase scan.^(12,13) Li *et al.* investigated dynamic CT scan with delayed portal venous phase in between the usual portal venous and delayed phase but it failed to detect well-differentiated HCC in cirrhosis.⁽⁷⁾ Lim *et al.* compared the value of the triple phase to the dual phase CT scan in detecting HCC.⁽¹⁸⁾ They reported that delayed phase scan can confirm diagnosis in an equivocal lesion. Although in our study, the dual phase study showed a high mean value of confidence level with positive diagnosis of HCC (4.28 and 4.45), and the addition of delayed phase showed significantly increased confidence level in the diagnosis of HCC ($P < .05$).

Furthermore, our study revealed that approximately one-fourth of HCC lesions showed enhancement on arterial phase, iso- or hyperdensity on portal venous phase and hypodensity on delayed phase which classified as wash out on delayed

phase pattern. We believe that these lesions can be confused or misdiagnosed with other hypervascular tumors if delayed phase scan is not performed. We also found higher percentages of this tumor group in small HCCs. We concluded that delayed phase was helpful in detecting small HCCs. Similar to the results of Monzawa *et al.*, small HCCs in cirrhosis were more conspicuous in delayed phase and they recommended performing dynamic CT scan with adding delayed phase.⁽¹⁹⁾ Lim *et al.* also reported that delayed phase shows better detection of small HCCs than portal venous phase.⁽¹⁸⁾ Iannaccone *et al.* supported the addition of delayed phase adjunct to the combination of hepatic arterial phase and portal venous phase in depicting HCC in cirrhotic patient.⁽¹⁶⁾

Moreover, delayed phase can show tumor capsule enhancement, resulting in a more detected tumor. Another important reason, capsular enhancement is an imaging finding of predicting massive necrosis of tumors after TACE. To our knowledge, there is no reported study about HCC that shows capsular enhancement. In our results, only 44 (40.4%) HCCs showed tumor capsule, which was more pronouncedly found in large HCC group (86.4%).

Of the 53 HCC patients, it is not surprising that 17 (32.1%) cases showed portal vein involvement and 1 (1.9%) case showed hepatic vein involvement. Five (9.4%) patients demonstrated arterioportal shunt.

A limitation of our study is the low number of lesions that have been pathologically proven. In clinical practice, hepatic nodules that have a radiographic appearance of typical enhancement pattern of HCC and AFP greater than 200 ng/dl are

further treated without requirement of pathological results, based on AASLD criteria. And, the nodules that are not consistent with this criterion, such as typical enhancement nodule in patient with AFP less than 200 ng/dl, do not mean these nodules are not HCC. So, these cases which we excluded from our study cannot be considered as negative for HCC. These are the reasons that sensitivity, specificity, positive and negative predictive values cannot be calculated.

Conclusion

In this study, CT findings on delayed phase scan such as wash out pattern and delayed capsular enhancement are helpful in the diagnosis of HCC, especially in small HCCs with a diameter of less than 2 cm. Furthermore, adding the delayed phase scan shows significantly increased confidence level and can confirm the diagnosis.

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