

Original paper

Prediction microvascular invasion of hepatocellular carcinoma based on tumour margin enhancing pattern in multiphase computed tomography images

Natthaphong Nimitrungsawee^{A,D,E,F}, Nakarin Inmutto^{A,B,C}, Amonlaya Amantakul^{A,F},
Attaporn Jantarangkoon^{B,F}

Department of Radiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Abstract

Purpose: The presence of microvascular invasion of hepatocellular carcinoma has a significantly decreased outcome following hepatectomy or liver transplantation. Currently, it is still based on histological examination. Identification of microvascular invasion by using pre-operative imaging is important for the decision-making of surgeons and interventional radiologists. Aim of the study was to predict the microvascular invasion of hepatocellular carcinoma based on tumour margin enhancement of pre-operative multiphase computed tomography (CT) images.

Material and methods: Fifty-three patients with hepatocellular carcinoma, who underwent pre-operative multiphase CT scans, were included in this study. Tumour margin enhancing patterns were analysed in the late arterial phase, portovenous phase, and delay phase. The CT features including peritumoral enhancement, arterial rim-enhancement, presence of daughter nodules, complete capsule enhancement in portovenous/delay phase, and nodular capsule enhancement in portovenous/delay phase were reviewed with calculations for sensitivity and specificity. Univariate analysis and multivariate analysis were used to identify predictive features for microvascular invasion (MVI).

Results: In the late arterial phase, peritumoral enhancement or the presence of daughter nodules were not predictors for MVI. Nodular capsule enhancement in the portovenous phase and delay phase were independent predictors for MVI with odds ratios of 29.25 and 33.09, respectively. The sensitivity and specificity for incomplete/nodular capsule enhancement in the portovenous phase were 69.23% and 96.86%, respectively. The sensitivity and specificity for incomplete/nodular capsule enhancement in the delay phase were 71.79% and 96.86%, respectively.

Conclusion: Nodular capsule enhancement in the portovenous phase or delay phase was a good predictor for MVI.

Key words: hepatocellular carcinoma, microvascular invasion, tumour margin, capsule enhancement, CT.

Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumour with a high mortality rate throughout the world. In 2018, the World Health Organization reported liver cancer to be the first cancer-related mortality rate and have second highest incidence rate of all cancers in Thailand [1].

The risk factors related to HCC in the general Thai people are chronic hepatitis B virus (HBV) infection, alcohol consumption, chronic hepatitis C virus (HCV) infection, and cryptogenic cirrhosis.

From many previous studies, we found that microvascular invasion (MVI) was related to the recurrence and survival rates in patients after surgical resection or liver

Correspondence address:

Nakarin Inmutto, Department of Radiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, e-mail: nakarin.i@cmu.ac.th

Authors' contribution:

A Study design · B Data collection · C Statistical analysis · D Data interpretation · E Manuscript preparation · F Literature search · G Funds collection

transplant [2-5]. Currently, many studies try to use multiple imaging modalities to detect MVI, such as computerized tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography (PET) scan. At present, the CT scan is a widely used diagnostic tool for diagnosis and pre-operative planning of HCC. Lim *et al.* [4] reported that disruption of the capsule by CT was correlated with tumour invasion. Another study by Chou *et al.* [6] reported that a non-smooth tumour margin is associated with MVI, but the pathology report is still the gold standard.

From the previous studies, pathologic findings of HCC fibrous capsule tend to protect the tumour invasion [3, 4, 7]. Therefore, some studies have attempted to use CT scans to detect fibrous capsules to predict MVI; however, the accuracy of CT scan for this detection was varied.

Therefore, the purpose of this research was to study the findings and accuracy for detecting MVI from CT scans.

Material and methods

Patients

This retrospective study at Maharaj Nakorn Chiang Mai Hospital was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Study Code: RAD-2563-07224), and informed consent was not required.

The inclusion criteria were as follows: pathological report of HCC from surgery by the Department of Pathology with a pre-operative CT scan in the picture archiving and communication system (PACS). Patients with age less than 15 years or evidence of macrovascular invasion were excluded from this study. During the period from January 2013 to August 2017, 53 patients were identified.

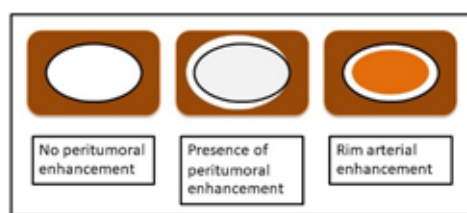


Figure 1. Illustration shows 3 patterns of peripheral enhancement on the arterial phase. No peritumoral enhancement, presence of peritumoral enhancement, and rim-arterial enhancement

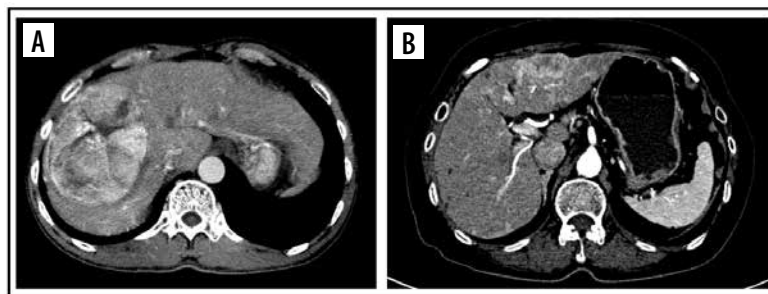


Figure 2. Computed tomography images of pattern enhancement on arterial phase. Peritumoral enhancement (A) and rim-enhancement (B)

Imaging acquisition

CT images of the liver were obtained with one of two multidetector CT scanners (SOMATOM FORCE and SOMATOM DEFINITION, Siemens Medical Solutions, Forchheim, Germany). The patients were in a supine position. The images were obtained in a craniocaudal direction. First, pre-contrast CT images of the liver were scanned. 100 ml of a non-ionic iodinated contrast media (350 mg/ml) were injected through the antecubital vein at 3-4 ml/s using a power injector. The hepatic arterial phase (HAP), portovenous phase (PVP), and delay phase (DP) of scanning began 35, 80, and 180 seconds after the injection of contrast media, respectively. Coronal and sagittal images were reconstructed with a 5-mm slice thickness using raw imaging data for portovenous-phase CT.

Imaging analysis

The CT image was reviewed on PACS and using a Synapse workstation, by a board-certificated diagnosis radiologist and a third-year resident training in radiology, based on consensus. The CT scan was evaluated depending on the phase.

The imaging features on HAP were classified as no peritumoral enhancement, presence of peritumoral enhancement, and rim-arterial enhancement. The peritumoral enhancement was defined as the existence of a detectable arterial-enhancing area adjacent to the tumour border on the arterial phase and became iso-enhanced similar to the liver parenchyma on the delay phase. Rim-arterial enhancement was a rim-like enhancement at the peripheral aspect of the tumour (Figures 1 and 2).

The tumour margin enhancement on PVP and DP were evaluated as capsule enhancement. The capsule was defined as a thin, linear, enhanced structure encasing the tumour. We classified capsule enhancement as one of four following groups: no capsule, complete smooth capsule, incomplete capsule, and nodular capsule enhancement. No capsule is defined as a non-visualized enhancement of the capsule. Complete smooth capsule enhancement was a smooth enhancement at the normal liver-tumour interface in all axial, coronal, and sagittal images. The incomplete capsule was an interrupted capsule enhancement

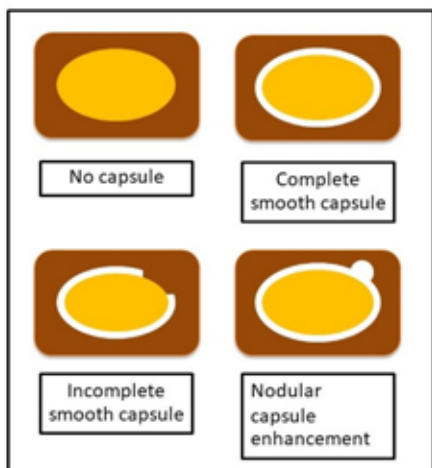


Figure 3. Illustration shows 4 patterns of capsule enhancement. No capsule, complete smooth capsule, incomplete capsule, and nodular capsule enhancement

without nodular appearance. Nodular capsule enhancement was a focal outgrowth of enhancing capsule protruding into the normal liver parenchyma (Figures 3 and 4).

Histopathological examination

The histopathological findings and MVI were recorded based on pathology reports. No re-examination of pathological slices was done. The degree of tumour differentiation was categorized according to the Edmondson-Steiner classification.

Statistical analyses

Statistical analyses were performed by using the software STATA ver.15.1. The quantitative data were as follows: age, size of the tumour, and interval time results, presented as mean and standard deviation or median and interquartile range depending on data distribution. Categorical variables, such as peritumoral enhancement, tumour capsule, daughter nodule, and background liver, were analysed by the chi-square test. The parameters found to have statistical significance by univariate analysis were entered into multivariate analysis. The parameters that showed statistical significance by multivariate analysis were calculated and presented as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Results

Patient characteristics

A total of 53 HCC patients were included in the study. Tables 1 and 2 summarize the CT imaging features and histological characteristics of patients in the MVI-present group and MVI-absent group.

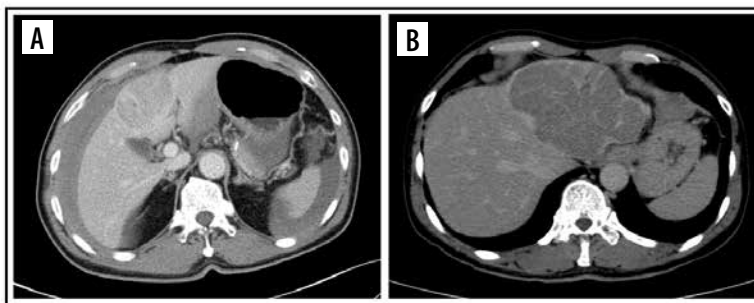


Figure 4. Computed tomography images of pattern enhancement on portovenous phase. Complete smooth capsule (A) and nodular capsule enhancement (B)

The mean age was 55.91 years and was comparable between the 2 groups. The background of liver cirrhosis found 64.15% of patients and comparable between the MVI present group and MVI absent group.

The mean tumour size at diagnosis detected by CT was significantly bigger in the MVI-present group than in the MVI-absent group (7.34 cm vs. 2.69 cm, $p = 0.001$).

Regarding histological features, HCCs with MVI and HCCs without MVI showed similar cell types and cell differentiation. Most of the HCCs showed a trabecular pattern; 76.67% of the MVI-present group and 66.67% of the MVI-absent group.

Computed tomography imaging features of the 2 groups

The presence of daughter nodules was uncommon in our study, at only 13.21%.

Peritumoral enhancement in HAP was seen in 11/33 (28.20%) in the MVI-present group versus 1/14 (7.14%) in the MVI-absent group. Rim arterial enhancement was seen in only one case in our study, 1.89%.

Nodular capsule enhancement in PVP was significantly more common in the MVI-present group than the MVI-absent group, at 66.67% versus 7.14%, respectively.

The nodular capsule enhancement in DP was seen 28/39 (71.79%) in the MVI-present group versus 1/14 (7.14%) in the MVI-absent group; the difference between the 2 groups was statistically significant.

In univariate analysis (Table 3), nodular capsule enhancement on PVP (odds ratio [OR] = 29.250; 95% confidence interval [CI]: 3.425-259.757; $p = 0.002$) and nodular capsule enhancement on DP (OR = 33.090; 95% CI: 3.853-284.138; $p = 0.001$) were significant independent predictors of MVI.

The sensitivity, specificity, accuracy, PPV, and NPV for significant imaging findings and their combination for predicting MVI are shown in Table 4.

Discussion

The presence of MVI in pathological specimens predicts the risk of tumour recurrence and long-term survival after surgery [7,8]. One study showed one-year recurrence

Table 1. Comparison of computed tomography imaging features according to microvascular invasion. Unless otherwise indicated, data are the number of patients with the percentage in parentheses. Categorical variables were compared by using the χ^2 test or Fisher exact test

CT imaging features	All patients (n = 53)	MVI present (n = 39)	MVI absent (n = 14)	p-value
Tumour size (cm)	6.11	7.34	2.69	0.001
Background liver				
Normal liver	19 (35.85)	15 (38.46)	4 (28.57)	0.508
Liver cirrhosis	34 (64.15)	24 (61.54)	10 (71.43)	
Daughter nodule				
Absent	46 (86.79)	32 (82.05)	14 (100.00)	0.089
Present	7 (13.21)	7 (17.95)	0	
Margin enhancement				
Arterial phase				
Non-rim enhancement	40 (75.47)	27 (69.23)	13 (92.86)	0.208
Peritumoral enhancement	12 (22.64)	11 (28.20)	1 (7.14)	
Rim enhancement	1 (1.89)	1 (2.57)	0 (0)	
Portovenous phase				
No capsule enhancement	21 (39.62)	10 (25.64)	11 (78.58)	0.001
Complete smooth capsule enhancement	4 (7.55)	3 (7.69)	1 (7.14)	
Incomplete capsule enhancement	1 (1.89)	0 (0)	1 (7.14)	
Nodular capsule enhancement	27 (50.94)	26 (66.67)	1 (7.14)	
Delay phase				
No capsule enhancement	15 (28.30)	6 (15.39)	9 (64.29)	0.000
Complete smooth capsule enhancement	8 (15.10)	5 (12.82)	3 (21.43)	
Incomplete capsule enhancement	1 (1.89)	0 (0)	1 (7.14)	
Nodular capsule enhancement	29 (54.71)	28 (71.79)	1 (7.14)	

CT – computed tomography, MVI – microvascular invasion. Significant p-value at < 0.050

Table 2. Comparison of histological features according to microvascular invasion. Unless otherwise indicated, data are the number of patients with the percentage in parentheses. Categorical variables were compared by using the χ^2 test or Fisher exact test

Histologic features	All patients (n = 42)	MVI present (n = 30)	MVI absent (n = 12)	p-value
Histologic type				
Trabecular	31 (73.80)	23 (76.67)	8 (66.67)	0.561
Clear	1 (2.40)	1 (3.33)	0 (0.00)	
Other	10 (23.80)	6 (20.00)	4 (33.33)	
Histological grade				
Well differentiated	8 (19.05)	5 (16.67)	3 (25.00)	0.758
Moderately differentiated	28 (66.67)	21 (70.00)	7 (58.33)	
Poorly differentiated	6 (14.28)	4 (13.33)	2 (16.67)	

MVI – microvascular invasion. Significant p-value at < 0.050

rates in a patient with and without MVI as 23.3% and 7.5%, respectively [9]. Li developed a nanogram using MVI as the predictive variable to predict lung metastasis [10]. So, the prediction of MVI on preoperative imaging is essential in clinical practices, including prognostic evaluation, choosing the width of margin in different treatment options (hepatectomy, transplantation, ablation, or transarterial

chemoembolization), and monitoring tumour recurrence. CT is widely used to evaluate patients with HCC. Therefore, it is acceptable to identify MVI by pre-operative CT.

Lee *et al.* demonstrated peritumoral enhancement and rim enhancement on the arterial phase of gadoteric acid-enhanced MRI, which was an independent and significant predictor of MVI [11]. Our study showed that

Table 3. Univariate and multivariate analyses of computed tomography imaging features in predicting microvascular invasion

Factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Tumour size	1.960	1.172, 3.275	0.010	1.533	0.887, 2.649	0.126
Present daughter nodule	N/A					
Peritumoral enhancement	5.107	0.594, 43.853	0.137			
PV smooth capsule enhancement	1.083	0.103, 11.363	0.947			
PV nodular capsule enhancement	29.250	3.425, 259.757	0.002	2.906	0.149, 56.335	0.480
Delay smooth capsule enhancement	0.539	0.110, 2.629	0.445			
Delay nodular capsule enhancement	33.090		0.001	6.057	0.344, 106.383	0.218

OR – odds ratio, CI – confidence interval, PV – portovenous. Significant p-value at < 0.050

Table 4. Diagnostic performance of computed tomography imaging features in predicting microvascular invasion. Data are presented as percentages. Data in parentheses are the number of subjects used to calculate the percentage

CT imaging features	Sensitivity	Specificity	Accuracy	PPV	NPV
Present daughter nodule	17.95	100	39.62	100	30.43
Peritumoral enhancement	28.21	92.86	45.28	91.67	31.71
Arterial rim enhancement	2.56	100	28.30	100	26.92
PV smooth capsule enhancement	7.69	92.86	30.19	75.00	26.53
PV nodular capsule enhancement	69.23	92.86	75.47	96.43	52.0
Delay smooth capsule enhancement	12.82	78.57	30.19	62.50	22.44
Delay nodular capsule enhancement	71.79	92.86	77.36	96.55	54.17

PPV – positive predictive value, NPV – negative predictive value, CT – computed tomography, PV – portovenous

peritumoral enhancement was an independent predictor of MVI with an OR of 5.107, but it was not statistically significant. The specificity of peritumoral enhancement and rim enhancement was greater than 90%, but the sensitivity was less than 30%. These arterial margin enhancement patterns were not statistically significant because of the small number of patients. The presence of daughter nodule was not a statistical calculation in our study either. Further study with more sample size is needed.

Peripheral enhancement surrounding hepatic nodule in PVP and DP represent capsule enhancement. The capsule enhancement in CT or MR images is one of the criteria for diagnosis of HCC in the Liver Imaging Reporting and Data System (LI-RADS) [12]. This capsule could be a fibrous capsule or pseudocapsule in histological findings. Previous studies found that capsule enhancement on imaging varied from 43% to 64% of cases [4]. Capsule enhancement was more frequently found in our study, i.e. 60.38% on PVP and 71.70% on DP. Furthermore, the result of our study was similar to that of Kim *et al.*, who reported that capsule enhancement was better visualized on DP than on PVP [13].

Many studies found that non-smooth capsule enhancement was a predictor of MVI [2,6,9,13-16]. A prospective study by Chou demonstrated that a non-smooth tumour margin correlated with the presence of MVI [3].

The univariate analysis in our study showed that nodular capsule enhancement on PVP and DP were associated with MVI. The nodular capsule enhancement on DP had a sensitivity of 71.79% and specificity of 92.86%.

Our study had several limitations. First, due to the retrospective study design, selection bias may have been present. Some small HCCs were not included in our study because the patient underwent radiofrequency ablation instead of surgery. Also some intermediate and advance HCCs were not included in our study because patients were not surgical candidates. Secondly, histological analysis was based on pathology reports without re-examination of pathological slides. Thirdly, our study was performed in an institution with a small sample size.

Conclusion

Peritumoral enhancement on arterial phase and nodular capsule enhancement on PVP and DP are CT findings used for the diagnosis of the presence of MVI with high specificity. The univariate analysis revealed that nodular capsule enhancement on PVP and DP were predictors of MVI.

Conflict of interest

The authors report no conflict of interest.

References

- Chonprasertsuk S, Vilaichone RK. Epidemiology and treatment of hepatocellular carcinoma in Thailand. *Jpn J Clin Oncol* 2017; 47: 294-297.
- Ahn SY, Lee JM, Joo I, et al. Prediction of microvascular invasion of hepatocellular carcinoma using gadoxetic acid-enhanced MR and 18F-FDG PET/CT. *Abdom Imaging* 2015; 40: 843-851.
- Chou CT, Chen RC, Lin WC, et al. Prediction of microvascular invasion of hepatocellular carcinoma: preoperative CT and histopathologic correlation. *Am J Roentgenol* 2014; 203: W253-W259. doi: 10.2214/AJR.13.10595.
- Lim JH, Choi D, Park CK, et al. Encapsulated hepatocellular carcinoma: CT-pathologic correlations. *Eur Radiol* 2006; 16: 2326-2333.
- Min JH, Lee MW, Park HS, et al. Interobserver variability and diagnostic performance of gadoxetic acid-enhanced MRI for predicting microvascular invasion in hepatocellular carcinoma. *Radiology* 2020; 297: 573-581.
- Chou C, Chen R, Lee C, et al. Prediction of microvascular invasion of hepatocellular carcinoma by pre-operative CT imaging. *Br J Radiol* 2012; 85: 778-783.
- Ünal E, Idilman IS, Akata D, et al. Microvascular invasion in hepatocellular carcinoma. *Diagn Interv Radiol* 2016; 22: 125-132.
- Zhang X, Li J, Shen F, Lau WY. Significance of presence of microvascular invasion in specimens obtained after surgical treatment of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2018; 33: 347-354.
- Yamashita Y, Tsujita E, Takeishi K, et al. Predictors for microinvasion of small hepatocellular carcinoma ≤ 2 cm. *Ann Surg Oncol* 2012; 19: 2027-2034.
- Li J, Zhou J, Yang PH, et al. Nomograms for survival prediction in patients undergoing liver resection for hepatitis B virus related early stage hepatocellular carcinoma. *Eur J Cancer* 2016; 62: 86-95.
- Lee S, Kim SH, Lee JE, et al. Preoperative gadoxetic acid-enhanced MRI for predicting microvascular invasion in patients with single hepatocellular carcinoma. *J Hepatol* 2017; 67: 526-534.
- Schima W, Heiken J. LI-RADS v2017 for liver nodules: how we read and report. *Cancer Imaging* 2018; 18: 14. doi: 10.1186/s40644-018-0149-5.
- Kim B, Lee JH, Kim JK, et al. The capsule appearance of hepatocellular carcinoma in gadoxetic acid-enhanced MR imaging: correlation with pathology and dynamic CT. *Medicine (Baltimore)* 2018; 97: e11142. doi: 10.1097/MD.00000000000011142.
- Chou CT, Chen RC, Lin WC, et al. Prediction of microvascular invasion of hepatocellular carcinoma: preoperative CT and histopathologic correlation. *AJR Am J Roentgenol* 2014; 203: W253-W259. doi: 10.2214/AJR.13.10595.
- Hu H, Zheng Q, Huang Y, et al. A non-smooth tumor margin on preoperative imaging assesses microvascular invasion of hepatocellular carcinoma: a systematic review and meta-analysis. *Sci Rep* 2017; 7: 15375. doi: 10.1038/s41598-017-15491-6.
- Huang M, Liao B, Xu P, et al. Prediction of microvascular invasion in hepatocellular carcinoma: preoperative Gd-EOB-DTPA-dynamic enhanced MRI and histopathological correlation. *Contrast Media Mol Imaging* 2018; 2018: 9674565. doi: 10.1155/2018/9674565.