Dynamic Contrast-Enhanced Computed Tomography Findings that may Predict Poorly-Differentiated Hepatocellular Carcinoma Prior to Treatment

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ABSTRACT

Objective: To identify CT findings that predict poorly-differentiated hepatocellular carcinoma (p-HCC).

Methods: This retrospective study included pathologically proven HCC patients during January 2010 to December 2017 who underwent dynamic contrast-enhanced computed tomography (CT) imaging within 12 weeks before the pathological diagnosis. CT findings were reviewed and graded by consensus opinion of two abdominal radiologists. The relationship between imaging findings and histological differentiation of HCC was analyzed using chi-square test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for diagnosis of p-HCC were calculated.

Results: Of 200 HCCs during the study period, 18 were well-differentiated, 170 were moderately-differentiated, and 12 were poorly differentiated. Irregular rim enhancement in arterial phase (p<0.001) and presence of lymphadenopathy (p=0.003) were both statistically significantly different among the three types of histological differentiation of HCC. Sensitivity, specificity, PPV, NPV, and accuracy for prediction of p-HCC by the presence of irregular rim enhancement in arterial phase and lymphadenopathy were 58.3%, 97.3%, 58.3%, 97.3%, and 95%, and 50%, 88.8%, 22.2%, 96.5%, and 86.5% - all respectively.

Conclusion: The presence of irregular rim enhancement in arterial phase and lymphadenopathy are potentially useful CT findings for prediction of p-HCC prior to treatment.

Keywords: Computed tomography; histological differentiation; poor differentiation; hepatocellular carcinoma (Siriraj Med J 2020; 72: 336-342)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant hepatic tumor, and it is a huge contributor to the world's cancer burden.[1] The treatment options for HCC include curative therapies (hepatic resection, liver transplantation, and ablative techniques such as radiofrequency/microwave ablation (RFA), percutaneous ethanol injection therapy (PEIT)), and noncurative therapies (transarterial chemoembolization (TACE), radioembolization, stereotactic body radiation therapy (SBRT) and molecularly targeted therapy).[2-4] The type of treatment depends on tumor staging, patient performance status, and liver function reserve.

RFA has grown quickly during the last decade and currently considered the treatment of choice for HCC patients with Barcelona-Clinic Liver Cancer (BCLC)

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stage 0-A who are not suitable for surgery. However, small (<2.5 cm) single tumor that is easily located may be treated by either resection or ablation.[4] Forner *et al.*[5] suggested RFA instead of resection in patients with early HCC (<2 cm.). Several studies[6-8] reported that histological grading of HCC is an important prognostic factor after treatment, and that poorly-differented lesions have the worse prognosis. It has also been reported that poor differentiation is a risk factor for tumor seeding after RFA.[9,10] Fukuda *et al.*[11] suggested that even solitary small HCC (up to 2 cm.), when hepatic function is well preserved, hepatic resection should be the first choice especially in cases of moderately or poorly differentiated HCC due to high frequency of microscopic vascular invasion. Therefore, the prediction of poorly differentiated HCC before treatment has potential benefit for treatment planning and for safe RFA even in patients with small HCC.

Currently, non-invasive diagnosis of HCC can be made by imaging characteristics on dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI).[2] Pathological diagnosis is reserved for suspicious lesions without characteristic imaging features. However, histological differentiation of HCC is not accurately obtained before surgery. Our review of the literature revealed that only a few studies[12-16] have investigated the relationship between imaging findings and histological grading of HCC.

Accordingly, the aim of this study was to investigate and identify dynamic contrast-enhanced CT findings that may predict poorly-differentiated hepatocellular carcinoma (p-HCC) prior to treatment.

MATERIALS AND METHODS

Study population

This retrospective single-center study was approved by the Siriraj Institutional Review Board (SIRB) (Si 226/2016) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The requirement to obtain written informed consent was waived. Patients with pathologically proven diagnosis of HCC during January 2010 to December 2017 were searched using pathological electronic database diagnosis. Patients who had no data relative to histological differentiation, who had not undergone dynamic CT within 12 weeks before the pathological diagnosis, who had received any prior treatment (e.g., RFA, TACE), and/or who had improper phases of dynamic CT were excluded. A flowchart showing the patient enrollment process is given in Fig 1. Our database search revealed 200 patients (151 males, and 49 females) with a pathologically proven diagnosis of HCC. The mean age of patients was 60.3±11.3 years (range: 30-93). The pathology diagnosis was obtained from core needle biopsy in 49 patients (24.5%), and from surgical resection in 151 patients (75.5%). The median time interval between CT imaging and pathological diagnosis was 31 days (range: 1-83).

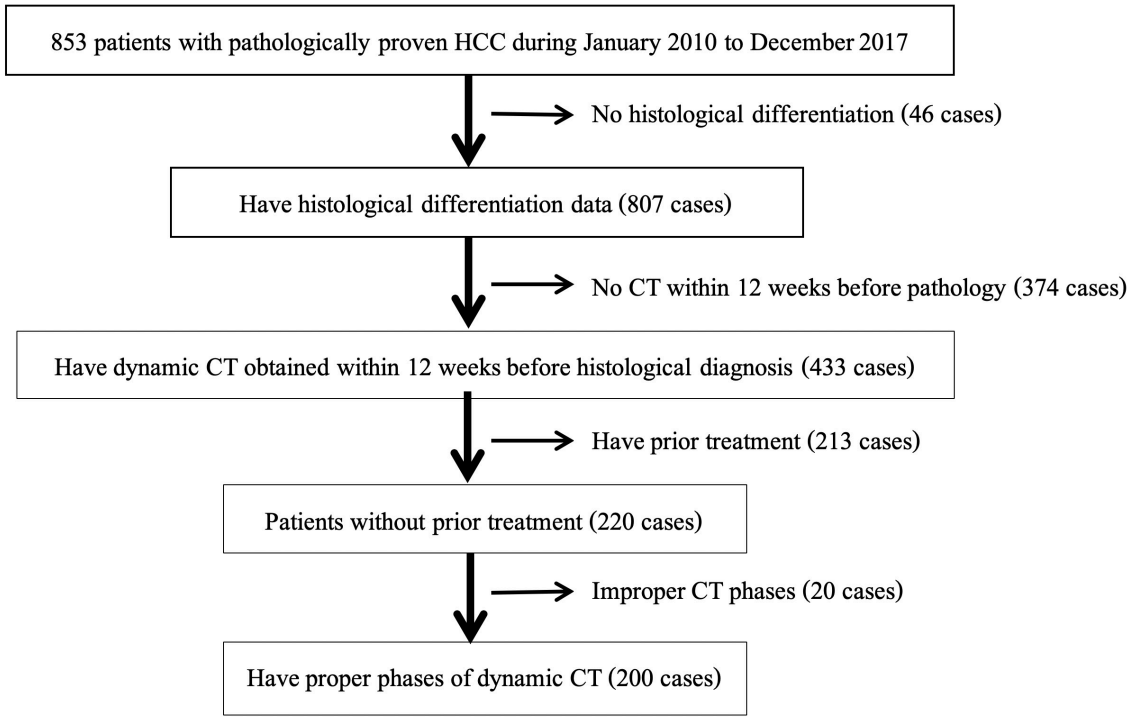


Fig 1. Flowchart describing the patient enrollment process.

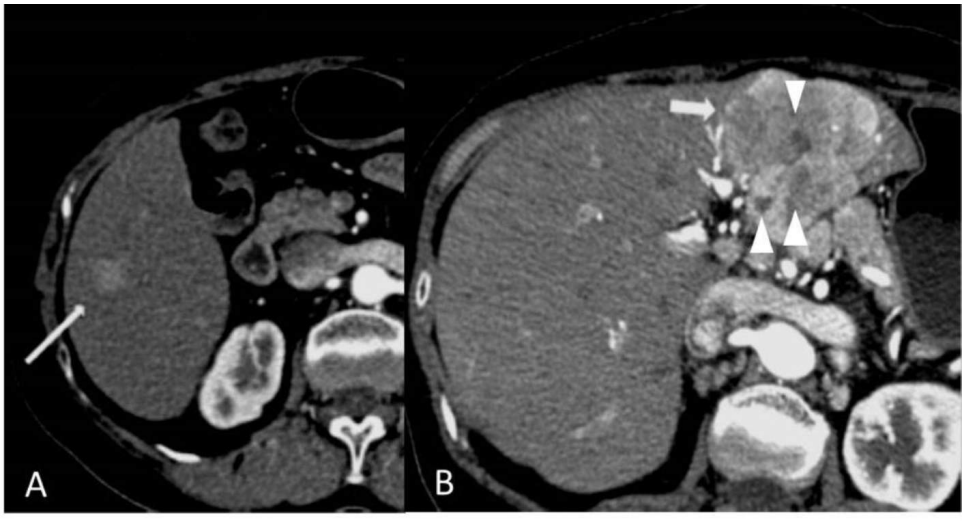
CT technique and interpretation

Dynamic CT scans of the liver were performed with a 16, 64, or 128 detector helical CT scanner (LightSpeed VCT, Discovery CT 750 HD and Optimal CT660; GE Healthcare, United States or SOMATOM Definition Dual Source, Siemens, Germany). The slice thickness was 1.25-1.5 mm (reconstructed at 5.0-7.0 mm). Dynamic contrast-enhanced CT scans were routinely performed during breath hold, including non-contrast, arterial dominant, and portovenous phases. Delayed phase was added in some patients. The arterial dominant, portovenous, and delayed phases were performed at 35 seconds, 80 seconds, and 5 minutes after initiation of contrast injection. Approximately 2 mL/kg of nonionic iodinated contrast agent followed by 20 mL of water was injected using a power injector at a rate of 2-3 mL/second.

CT images were retrospectively reviewed and graded by consensus opinion by two abdominal radiologists with 16 years and 13 years of experience, respectively. Types or levels of differentiation of HCC included well-differentiated (w-HCC), moderately-differentiated (m-HCC), and poorly-differentiated (p-HCC). Both readers were blinded to pathological differentiation data and other clinical characteristics, and knew only that the patient had been definitively diagnosed with HCC. For cases with multiple tumors, the largest lesion at the location of pathological diagnosis was assessed. CT findings were assessed, as follows: number of tumor(s) (single or multiple), tumor size (measurement of maximal diameter, including capsules), tumor margin (smooth, irregular, or infiltrative), tumor attenuation on pre-contrast images, degree of tumor enhancement (arterial enhancement, hypovascular enhancement), enhancement pattern on arterial phase (homogenous, heterogenous (Fig 2)), presence of non-enhanced area on arterial phase (Fig 2&3), presence of irregular rim enhancement on arterial phase (Fig 4), tumor stain washout on portovenous or delayed phases (Fig 3), capsular enhancement, lymphadenopathy (lymph node enlargement of >1 cm in short axis diameter), and vascular invasion.

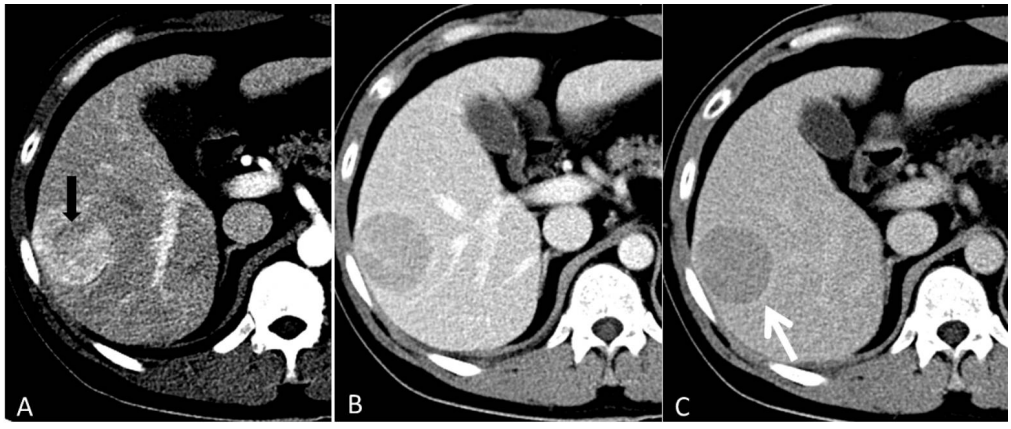
Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Normally distributed continuous data, including age and tumor size, are presented as mean ± standard deviation. Non-normally distributed continuous data, such as time interval between CT imaging and pathological diagnosis of HCC, are given as median and range. Categorical data are shown as frequency and percentage. The relationship of CT findings among the three types of histologic differentiation of HCC was analyzed using chi-square test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for diagnosis of p-HCC were calculated according to significant findings on dynamic contrast-enhanced CT. Statistical significance was defined as a *p*-value less than 0.05. All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA).



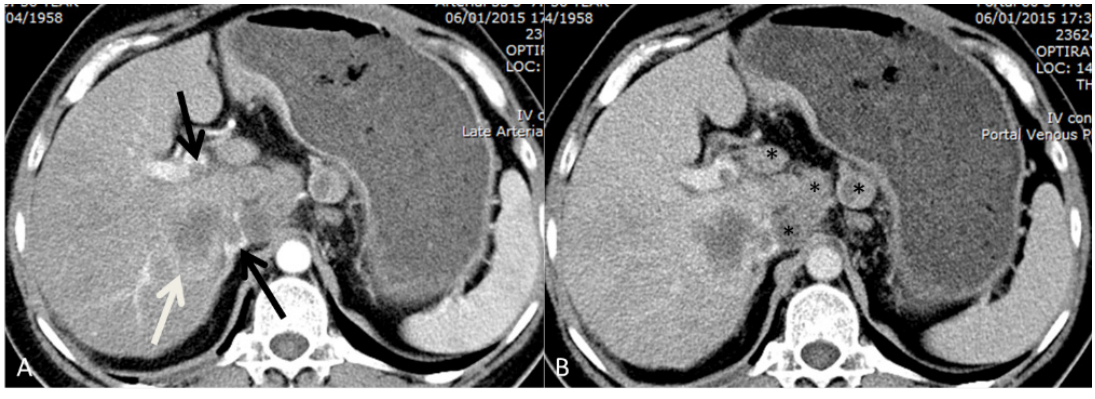
A. Axial CT image of arterial phase showing homogenous arterial enhanced HCC in right hepatic lobe without non-enhanced area (arrow).
B. Axial CT image of arterial phase (different case) showing heterogenous arterial enhanced HCC in left hepatic lobe (arrow) with presence of non-enhanced area (arrowhead).

Fig 2. Two different cases of arterial enhancement without non-enhanced area and arterial enhancement with non-enhanced area.



A. Axial CT image - arterial phase showing the presence of non-enhanced area on arterial phase (black arrow)
B. Axial CT image – portovenous phase showing tumor stain washout
C. Axial CT image – delayed phase showing tumor stain washout and the presence of capsular enhancement (white arrow)

Fig 3. Dynamic contrast-enhanced CT of a moderately-differentiated HCC case (pathological diagnosis from surgical resection).



Axial CT images of arterial phase (A) and portovenous phase (B) showing the presence of irregular rim enhancement on arterial phase (white arrow), and multiple abdominal lymphadenopathies (asterisk). Vascular invasion into portal vein and IVC was also demonstrated (black arrow).

Fig 4. Dynamic contrast-enhanced CT of a poorly-differentiated HCC case (pathological diagnosis from core needle biopsy).

RESULTS

Of 200 HCC cases, 120 cases (60%) had single lesion and 80 cases (40%) had multiple lesions. The histological classification was w-HCC in 18 cases (9%), m-HCC in 170 (85%) cases, and p-HCC in 12 cases (6%). There was no statistically significant difference in mean tumor diameter, type of tumor margin, tumor attenuation on pre-contrast image, pattern of tumor enhancement, presence of non-enhanced area on arterial phase, tumor stain washout, capsular enhancement, or vascular invasion among the three types of histological differentiation of HCC, as shown in Table 1. Hypovascular enhancement pattern was found in three cases (1.5%). All cases of p-HCC in the present study showed hypoattenuation on pre-contrast images, heterogenous arterial enhancement, presence of non-enhanced area on arterial phase, and tumor stain washout.

The present study found irregular rim enhancement (p<0.001) and presence of lymphadenopathy (p=0.003) to be statistically significantly different among the three types of histological differentiation of HCC (Table 1). The percentage of presence of irregular rim enhancement was significantly higher as the histological differentiation grade advanced. Lymphadenopathy was more commonly observed in p-HCC (50%) than in w-HCC (11.1%) and m-HCC (11.2%).

The sensitivity, specificity, PPV, NPV, and accuracy for the prediction of p-HCC by irregular rim enhancement and lymphadenopathy are shown in Table 2. Irregular rim enhancement had higher specificity, NPV, and accuracy (97.3%, 97.3%, and 95%, respectively) than lymphadenopathy (88.8%, 96.5%, and 86.5%, respectively) for p-HCC. The accuracy for prediction of p-HCC by combining these two findings did not significantly improve diagnosis compared to irregular rim enhancement alone, but the sensitivity was decreased to 33.3%.

TABLE 1. Correlation between CT findings and histological differentiation of HCC

CT findings	Histologically differentiation			*p*-value[a]	95% CI
	w-HCC (n=18)	m-HCC (n=170)	p-HCC (n=12)		
Tumor size; mean diameter ± SD	**6.5 ± 4.4 cm**	**5.3 ± 3.9 cm**	**6.3 ± 3.4 cm**	**0.524**	
Tumor margin				0.147	
Irregular	16 (88.9%)	132 (77.6%)	11 (91.7%)		
Smooth	1 (5.6%)	37 (21.8%)	1 (8.3%)		
Infiltrative	1 (5.6%)	1 (0.6%)	0 (0.0%)		
Tumor attenuation on pre-contrast images				0.232	
Hypoattenuation	13 (72.2%)	152 (89.4%)	12 (100%)		
Isoattenuation	2 (11.1%)	10 (5.9%)	0 (0.0%)		
Hyperattenuation	3 (16.7%)	7 (4.1%)	0 (0.0%)		
Fat content	0 (0.0%)	1 (0.6%)	0 (0.0%)		
Degree of tumor enhancement				1.0	
Arterial enhancement	18 (100%)	167 (98.2%)	12 (100%)		
Hypovascular enhancement	0 (0.0%)	3 (1.8%)	0 (0.0%)		
Enhancement pattern on arterial phase[b]				0.232	
Heterogeneous	17 (94.4%)	143 (85.6%)	12 (100%)		
Homogeneous	1 (5.6%)	24 (14.4%)	0 (0.0%)		
Non-enhanced area on arterial phase[b]				0.077	
Present	16 (88.9%)	125 (74.9%)	12 (100%)		
Absent	2 (11.1%)	42 (25.1%)	0 (0.0%)		
Irregular rim enhancement[b]				***<0.001***	
Present	0 (0.0%)	5 (3.0%)	7 (58.3%)		
Absent	18 (100%)	162 (97%)	5 (41.7%)		
Tumor stain washout[b]				0.858	
Present	17 (94.4%)	158 (94.6%)	12 (100%)		
Absent	1 (5.6%)	9 (5.4%)	0 (0.0%)		
Capsular enhancement				0.734	
Present	7 (38.9%)	55 (32.4%)	3 (25.0%)		
Absent	11 (61.1%)	115 (67.6%)	9 (75.0%)		
Lymphadenopathy				***0.003***	
Present	2 (11.1%)	19 (11.2%)	6 (50.0%)		
Absent	16 (88.9%)	151 (88.8%)	6 (50.0%)		
Vascular invasion				0.483	
Present	3 (16.7%)	22 (12.9%)	3 (25.0%)		
Absent	15 (83.3%)	148 (87.1%)	9 (75.0%)		

[a]Among the three different types of histologic differentiation in HCC, [b] Does not included three cases of hypovascular enhancement
Abbreviations: CT, computed tomography; HCC, hepatocellular carcinoma; w-HCC, well-differentiated HCC; m-HCC, moderately-differentiated HCC; p-HCC, poorly-differentiated HCC; SD, standard deviation

TABLE 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for prediction of p-HCC using CT findings.

CT findings	Sensitivity	Specificity	PPV	NPV	Accuracy
Irregular rim enhancement	58.3%	97.3%	58.3%	97.3%	95%
Lymphadenopathy	50.0%	88.8%	22.2%	96.5%	86.5%
Coexisting irregular rim enhancement and lymphadenopathy	33.3%	98.4%	57.1%	95.8%	94.4%

Abbreviations: p-HCC, poorly-differentiated hepatocellular carcinoma; CT, computed tomography

DISCUSSION

Histological grading of HCC is a relevant prognostic factor after treatment[6-8], and some studies found that poor differentiation is a risk factor of tumor seeding after RFA.[9,10] However, pathological diagnosis of HCC is not usually obtained before surgery, and needle biopsy is not routinely performed because of the risk of tumor seeding and the probability of diagnostic error due to tumor heterogeneity. Therefore, investigation into the correlation between imaging findings and histological grading of HCC might have some potential benefit for management of HCC patients.

Our study found that irregular rim enhancement on arterial phase had high specificity (97.3%) for prediction of p-HCC. This is similar to the findings of Kawamura, *et al.*[15] who found heterogeneous enhancement with irregular ring-like structures in the arterial phase to be an independent predictor of p-HCC. The explanation of this enhancement pattern may be combination of tumor necrosis and other factors, such as type II vessels[15]; however, the exact mechanism remains unknown. Nakachi, *et al.*[13] reported that arterial enhancement with non-enhanced areas, which included irregular rim enhancement pattern, was associated with p-HCC. Non-enhanced area on arterial phase and irregular rim enhancement on arterial phase were separately investigated in our study. Although non-enhanced area on arterial phase was present in all p-HCC in our study, this finding was not significantly difference among the three types of histological differentiation of HCC. This difference compared to prior study might be due to the small number of p-HCC and the relatively larger mean tumor size (5.5±3.9 cm. for all HCC cases) in our study. Tumor size is a factor that may affect enhancement pattern of HCC. Yoon SH, *et al.*[16] reported that tumor size <2 cm and w-HCC frequently had atypical enhancement patterns.

Irregular rim arterial enhancement pattern can also be found in other hepatic tumors, such as cholangiocarcinoma and fibrolamellar HCC. However, cholangiocarcinoma is rare in chronic hepatitis or cirrhotic patients when compared with HCC. Some imaging features can help in differentiating intrahepatic cholangiocarcinoma (ICC) from HCC.[17] ICC exhibits rim-like peripheral arterial enhancement with progressive centripetal enhancement, and it usually associates with peripheral biliary dilatation or capsular retraction. On the other hand, presence of intralesional fat and enhanced capsule are more suggestive of HCC than ICC. Fibrolamellar HCC, which is a rare primary liver tumor, has clinicopathologic features different from conventional HCC. It predominantly occurs in young patients without underlying hepatitis or cirrhosis, and serum alfa-fetoproteins are not elevated in most cases.[18] Calcification and central stellate scar are commonly seen in fibrolamellar HCC.[18] Presence of intralesional fat is more suggestive of conventional HCC than of fibrolamellar HCC.[18]

Abdominal lymph node is one of three most common sites of extrahepatic metastatic HCC.[19] In our study, lymphadenopathy was more commonly present in p-HCC (50%) than in w-HCC or m-HCC, and it had a specificity of 88.8% for prediction of p-HCC. This finding is similar to that reported by Lee, *et al.*[20] who found HCC with lymph node metastasis to be significantly associated with worse histological grade. However, the use of lymph node size criteria did not improve the accuracy of detection of metastatic nodes in our study. Enlarged lymph nodes can be either benign or metastatic nodes, and lymph node metastasis can be found in normal sized nodes. Further non-invasive imaging study for accurate evaluation of metastatic nodes is needed.

Tumor stain washout in the portovenous phase was reported to be associated with p-HCC in prior study.[13]

Lee, *et al.*[12] reported that early washout favored m-HCC and p-HCC more than w-HCC, and the presence of intratumoral aneurysm was highly specific finding for p-HCC. However, tumor stain washout was not found to be significant different among the three histological grades of HCC in our study.

Limitations

Our study has some limitations. First, this was a retrospective study and there was selection bias related to the inclusion criteria that only patients with pathological proof and CT images obtained within 12 weeks were selected. Second, the pathological diagnosis included patients with needle biopsy samples which can lead to diagnostic error due to heterogeneity of HCC tumors. Third, the small numbers of w-HCC (18 cases) and p-HCC (12 cases) in our study may reduce the reliability of the analysis. In the future, a larger scale cohort investigation should be conducted.

CONCLUSION

There is potential benefit of dynamic contrast-enhanced CT for prediction of p-HCC. The presence of irregular rim enhancement in arterial phase and lymphadenopathy are potentially useful CT findings for prediction of p-HCC prior to treatment.

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REFERENCES

1. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015;19:223-38.
2. Yu SJ. A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010-2016. Clin Mol Hepatol 2016;22:7-17.
3. Raza A, Sood GK. Hepatocellular carcinoma review: current treatment, and evidence-based medicine. World J Gastroenterol 2014;20:4115-27.
4. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Fin RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Disease. Hepatology 2018;68:723-50.
5. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245-55.
6. Tamura S, Kato T, Berho M, Misiakos EP, O'Brien C, Reddy KR, et al. Impact of histological grade of hepatocellular carcinoma on the outcome of liver transplantation. Arch Surg 2001;136:25-30.
7. Oishi K, Itamoto T, Amano H, Fukuda S, Ohdan H, Tashiro H, et al. Clinicopathologic features of poorly differentiated hepatocellular carcinoma. J Surg Oncol 2007;95:311-6.
8. Kim SH, Lim HK, Choi D, Lee WJ, Kim MJ, Kim CK, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma: effect of histologic grade on therapeutic results. AJR Am J Roentgenol 2006;186:S327-S33.
9. Imamura J, Tateishi R, Shiina S, Goto E, Sato T, Ohki T, et al. Neoplastic seeding after radiofrequency ablation for hepatocellular carcinoma. Am J Gastroenterol 2008; 103:3057-62.
10. Takada Y, Kurata M, Ohkohchi N. Rapid and aggressive recurrence accompanied by portal tumor thrombus after radiofrequency ablation for hepatocellular carcinoma. Int J Clin Oncol 2003;8:332-5.
11. Fukuda S, Itamoto T, Nakahara H, Kohashi T, Ohdan H, Hino H, et al. Clinicopathologic features and prognostic factors of resected solitary small-sized hepatocellular carcinoma. Hepatogastroenterology 2005;52:1163-7.
12. Lee JH, Lee JM, Kim SJ, Baek JH, Yun SH, Kim KW, et al. Enhancement patterns of hepatocellular carcinomas on multiphasicmultidetector row CT: comparison with pathological differentiation. Br J Radiol 2012;85:e573-83.
13. Nakachi K, Tamai H, Mori Y, Shingaki N, Moribata K, Deguchi H, et al. Prediction of poorly differentiated hepatocellular carcinoma using contrast computed tomography. Cancer Imaging 2014;14:7-12.
14. Asayama Y, Yoshimitsu K, Nishihara Y, Irie H, Aishima S, Taketomi A, et al. Arterial blood supply of hepatocellular carcinoma and histologic grading: radiologic-pathologic correlation. AJR Am J Roentgenol 2008;190:W28-W34.
15. Kawamura Y, Ikeda K, Hirakawa M, Yatsuji H, Sezaki H, Hosaka T, et al. New classification of dynamic computed tomography images predictive of malignant characteristics of hepatocellular carcinoma. Hepatol Res 2010;40:1006-14.
16. Yoon SH, Lee JM, So YH, Hong SH, Kim SJ, Han JK, et al. Multiphasic MDCT enhancement pattern of hepatocellular carcinoma smaller than 3 cm in diameter: tumor size and cellular differentiation. AJR Am J Roentgenol 2009;193:W482-9.
17. Seo N, Kim DY, Choi JY. Cross-sectional imaging of intrahepatic cholangiocarcinoma: development, growth, spread, and prognosis. AJR Am J Roentgenol 2017;209:W64-75.
18. Ganeshan D, Szklaruk J, Kundra V, Kaseb A, Rashid A, Elsayes KM. Imaging features of fibrolamellar hepatocellular carcinoma. AJR Am J Roentgenol 2014;202:544-52.
19. Katyal S, Oliver JH 3rd, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. Radiology 2000;216:698-703.
20. Lee CW, Chan KM, Lee CF, Yu MC, Lee WC, Wu TJ, et al. Hepatic resection for hepatocellular carcinoma with lymph node metastasis: clinicopathological analysis and survival outcome. Asian J Surg 2011;34:53-62.