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ORIGINAL ARTICLE

Retrospective Study

# Validated preoperative computed tomography risk estimation for postoperative hepatocellular carcinoma recurrence

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## Abstract

### *AIM*

To develop and validate a risk estimation of tumor recurrence following curative resection of operable hepatocellular carcinoma (HCC).

### *METHODS*

Data for 128 patients with operable HCC (according to Barcelona Clinic Liver Cancer imaging criteria) who underwent preoperative computed tomography (CT) evaluation at our hospital from May 1, 2013 through May 30, 2014 were included in this study. Follow-up data were obtained from hospital medical records. Follow-up data through May 30, 2016 were used to retrospectively analyze preoperative multiphasic CT

findings, surgical histopathology results, and serum α-fetoprotein and thymidine kinase-1 levels. The $\chi^2$ test, independent *t*-test, and Mann-Whitney *U* test were used to analyze data. A *P*-value of < 0.05 was considered statistically significant.

***RESULTS***

During the follow-up period, 38 of 128 patients (29.7%) had a postoperative HCC recurrence. Microvascular invasion (MVI) was associated with HCC recurrence ($\chi^2$ = 13.253, *P* < 0.001). Despite postoperative antiviral therapy and chemotherapy, 22 of 44 patients with MVI experienced recurrence after surgical resection. The presence of MVI was 57.9% sensitive, 75.6% specific and 70.3% accurate in predicting postoperative recurrence. Of 84 tumors without MVI, univariate analysis confirmed that tumor margins, tumor margin grade, and tumor capsule detection on multiphasic CT were associated with HCC recurrence (*P* < 0.05). Univariate analyses showed no difference between groups with respect to hepatic capsular invasion, Ki-67 proliferation marker value, Edmondson-Steiner grade, largest tumor diameter, necrosis, arterial phase enhanced ratio, portovenous phase enhanced ratio, peritumoral enhancement, or serum α-fetoprotein level.

***CONCLUSION***

Non-smooth tumor margins, incomplete tumor capsules and missing tumor capsules correlated with postoperative HCC recurrence. HCC recurrence following curative resection may be predicted using CT.

**Key words:** Hepatocellular carcinoma; Microvascular invasion; Computed tomography; Recurrence; Tumor margin; Tumor capsule



**Core tip:** We discuss risk estimation for recurrence following curative resection of operable hepatocellular carcinoma that meets Barcelona Clinic Liver Cancer imaging criteria. Preoperative multiphasic computed tomography findings, including non-smooth tumor margins, incomplete tumor capsule and missing tumor capsule, can predict hepatocellular carcinoma recurrence following curative resection. Treatment should include wide margins during curative resection, followed by antiviral therapy and chemotherapy.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-related death worldwide[1-3]. Surgical resection and liver transplantation are potentially curative treatment options for patients with HCC[4]. However, the 5-year HCC recurrence rate may be as high as 70%[5]. Recent studies have shown that tumor size and number[6], microvascular invasion (MVI)[5,7-9] and α-fetoprotein (AFP) levels[10,11] are associated with recurrence following surgical resection. Although many potential risk factors for HCC postoperative recurrence have been described, a reliable preoperative method to estimate this risk has not been established.

Kanai *et al*[12] first described nodular HCC sub-classification based on microscopic, clinical and prognostic features; these being single nodular type, single nodular type with extra-nodular growth, and contiguous multinodular type. Studies have shown that non-smooth tumor margins are associated with increased MVI[13-16]. Although computed tomography (CT) examination is part of the standard of care for HCC evaluation, no study has demonstrated the validity of preoperative CT assessment to predict postoperative recurrence of solitary HCC.

Thymidine kinase 1 (TK1), a DNA synthesis enzyme, is an important serum proliferation marker that correlates with clinical stage and is an independent prognostic factor for recurrence-free survival in HCC[17-20]. However, to our knowledge, there are no reports about serum TK1 levels and postoperative HCC recurrence.

In this study, we retrospectively assessed whether preoperative CT findings could predict postoperative HCC recurrence. We specifically evaluated largest tumor diameter, tumor margins, tumor capsule, necrosis, peritumoral enhancement, tumor enhanced ratio and hepatic capsular invasion. Furthermore, we assessed whether MVI, serum AFP, and serum TK1 levels were correlated with postoperative recurrence of solitary HCC.

## MATERIALS AND METHODS

### *Patients*

This retrospective study included 128 patients (105 males and 23 females), aged 24 to 79 years (mean, 47.7 years), with operable HCC (according to the Barcelona Clinic Liver Cancer imaging criteria) who underwent preoperative CT evaluation at our hospital from May 1, 2013 through May 30, 2014. Follow-up data were obtained from hospital medical records. HCC recurrence was defined as a pathologic or radiologic diagnosis of recurrent HCC during the follow-up period that ended on May 30, 2016. All patients

in this study: (1) had no cancer-related treatment or liver biopsy prior to CT imaging; (2) underwent partial hepatectomy and had HCC diagnosis confirmed by histopathology; (3) had no macrovascular invasion or metastasis on CT imaging; and (4) had livers with a Child-Pugh classification of A or B. This study was approved by our hospital institutional review board and all patients provided written informed consent.

### CT imaging protocol

Hepatic CT images were obtained using a 64-MDCT scanner (SOMATOM Sensation 64; Siemens, Forchheim, Germany) with Z-axis modulation, a spiral pitch of 1, a 5 mm section thickness, a 2 mm reconstruction gap, a field of view of 311 mm, 120 kVp, 230 mA, and a standard reconstruction algorithm. Nonionic contrast medium (300 mg I/mL iopromide) was administered at an injection rate of 3 mL/s for a total dose of 100 mL. For the hepatic arterial and portovenous phases, scanning was begun approximately 25 and 60 s after contrast media injection, respectively. Equilibrium phase images were acquired approximately 180 s after contrast media injection. The scanning range was the whole-liver zone while patients held their breath. Coronary and sagittal images were reconstructed with 5 mm section thickness.

### Image evaluation

Tumor margins on the liver map (*i.e.* transverse, coronary and sagittal planes) were defined as three subtypes (smooth margin, non-smooth margin focal extranodular and non-smooth margin multinodular), based on previous reports[12-16,21,22]. The tumor margins were categorized into one of the following three grades: Grade 0: smooth margin; Grade 1: focal extranodular type; and Grade 2: multinodular type. The tumor capsule was defined as a linear and enhanced structure surrounding the tumor detected by equilibrium phase CT imaging. Tumor capsules were categorized into the following three groups: Grade 0: complete tumor encapsulation; Grade 1: incomplete tumor encapsulation; and Grade 2: no tumor encapsulation. Negative or positive peritumoral enhancement was determined by multi-phase CT imaging. Positive peritumoral enhancement was defined in comparison to liver parenchyma as a hyperdense area proximal to the tumor border during arterial phase imaging that changed to an isodense area during equilibrium phase imaging. The tumor enhanced ratio was calculated as ($CT_{enhanced}$-$CT_{unenhanced}$)/$CT_{unenhanced}$.

All CT findings were reviewed by two radiologists experienced in liver CT evaluation: Lai SL (22 years of experience) and Xie D (21 years of experience). In the case of disagreements over CT findings, a third radiologist helped resolve discrepancies to achieve consensus.

### Serum samples and histopathologic analysis

The serum TK1 assay was performed using a commercial kit, based on an enhanced chemiluminescence dot blot assay. Serum AFP detection was carried out using enzyme immunoassay. Ki67 expression, hepatic capsular invasion and MVI were confirmed by immunohistochemistry. The Edmondson-Steiner (E-S) grade was determined using the WHO Liver Cancer Study Group guidelines[23].

### Statical analysis

Statistical analysis was performed using SPSS version 16.0 statistical software (SPSS, Chicago, IL, United States). An independent *t*-test was used to compare recurrence and non-recurrence groups with respect to largest tumor diameter, arterial phase enhanced ratio, portovenous phase enhanced ratio, serum AFP, serum TK1 and Ki67. Receiver operating characteristic curve analyses were used to determine the optimal cut-off value and diagnostic performance for $P < 0.05$. The chi-square test was used to compare tumor margins, necrosis, peritumoral enhancement, MVI and hepatic capsular invasion between groups. The tumor margin grade, E-S grade and tumor capsule were analyzed using the Mann-Whitney *U* test. A *P*-value of less than 0.05 was considered statistically significant.

## RESULTS

Quantitative and qualitative findings are summarized in Table 1. MVI was higher in the recurrence group (22 of 38 patients) compared to the non-recurrence group (22 of 90 patients) ($\chi^2 = 13.253$, $P < 0.001$). Despite antiviral therapy and chemotherapy during follow-up, 22 of 44 patients with MVI experienced recurrence after surgical resection. The presence of MVI was 57.9% sensitive, 75.6% specific and 70.3% accurate in predicting postoperative recurrence.

Of 84 recurrences without MVI, univariate analyses showed no difference between groups with respect to hepatic capsular invasion ($\chi^2 = 1.691$, $P = 0.193$), Ki67 value ($P = 0.686$), E-S grade ($Z = -0.460$, $P = 0.646$), largest tumor diameter ($P = 0.366$), necrosis ($\chi^2 = 0.412$, $P = 0.521$), arterial phase enhanced ratio ($P = 0.725$), portovenous phase enhanced ratio ($P = 0.685$), peritumoral enhancement ($P = 0.240$) or serum AFP level ($P = 0.882$). In 27 of 84 recurrences without MVI, serum TK1 did not differ between groups ($P = 0.377$). Univariate analyses showed that non-smooth tumor margins ($\chi^2 = 5.042$, $P = 0.025$), tumor margin grade ($Z = -2.355$, $P = 0.019$) and absence of tumor capsule on CT ($Z = -2.279$, $P = 0.023$) were

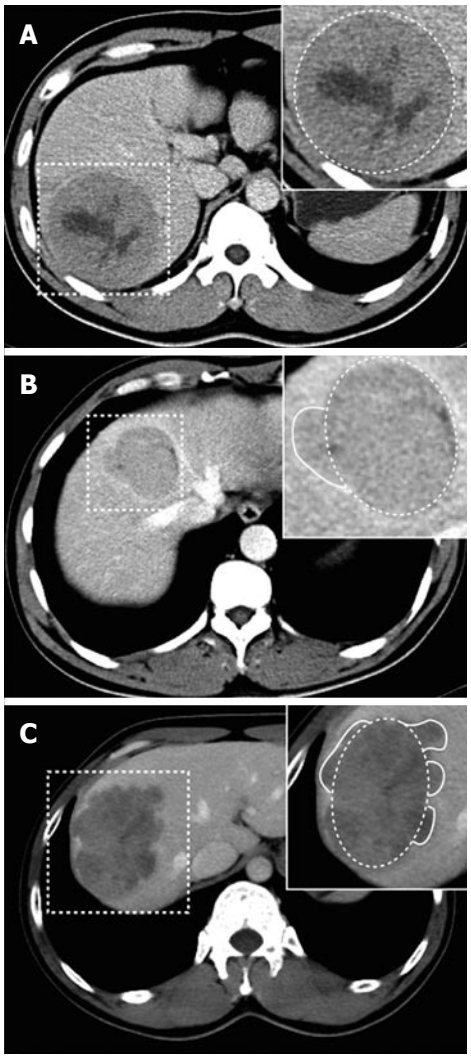


**Figure 1 Tumor margins on the liver computed tomography map.** A: Portovenous phase CT showing smooth margin at liver segment VI in a 36-year-old male patient without postoperative recurrence (dashed box); B: Portovenous phase CT showing focal extranodular type at liver segments V and VIII in a 38-year-old female patient with postoperative recurrence (dashed box); C: Portovenous phase CT showing multinodular type at liver segments V and VI in a 35-year-old male patient with postoperative recurrence (dashed box). CT: Computed tomography.

correlated with tumor recurrence (Figure 1A-C and Figure 2A-C).

## DISCUSSION

Surgical resection of HCC suffers from high rates of tumor recurrence[5]. A reliable and validated prognostic method to estimate individual HCC recurrence risk would help guide future treatment strategies. Factors commonly associated with high risk for postoperative HCC recurrence include tumor vascular invasion and poorly differentiated tumor grade[24]. In this study, however, E-S grade was not associated with tumor recurrence. We did confirm, however, that MVI may be a powerful independent prognostic factor for postoperative recurrence and metastasis[5,7,14,25-27].

**Table 1 Quantitative and qualitative factors associated with recurrence of hepatocellular carcinoma following curative resection**

| Risk factor | | Follow-up recurrence | | *P* value |
|---|---|---|---|---|
| | | Yes | No | |
| MVI | Positive | 22 | 22 | 0.000[b] |
| | Negative | 16 | 68 | |
| MVI-negative cases | | | | |
| Hepatic capsular invasion | Positive | 4 | 29 | 0.193 |
| | Negative | 12 | 39 | |
| Ki67 | | 30.3 ± 20.4 | 28.0 ± 21.0 | 0.686 |
| E-S grade[1] | I | 1 | 6 | 0.646 |
| | II | 8 | 36 | |
| | III | 7 | 26 | |
| Largest tumor diameter, cm | | 5.5 ± 3.0 | 4.8 ± 2.6 | 0.366 |
| Arterial phase enhanced ratio | | 0.62 ± 0.34 | 0.66 ± 0.40 | 0.725 |
| Portovenous phase enhanced ratio | | 0.77 ± 0.23 | 0.80 ± 0.33 | 0.685 |
| Tumor capsule | Complete | 3 | 35 | 0.023[a] |
| | Incomplete | 7 | 19 | |
| | Negative | 6 | 14 | |
| Necrosis | Positive | 8 | 28 | 0.521 |
| | Negative | 8 | 40 | |
| Tumor margins | Smooth | 9 | 56 | 0.019[a] |
| | Focal extranodular | 5 | 11 | |
| | Multinodular | 2 | 1 | |
| Peritumoral enhancement | Positive | 2 | 3 | 0.24 |
| | Negative | 14 | 65 | |
| AFP, ng/mL | | 336.8 ± 480.4 | 357.6 ± 505.6 | 0.882 |
| TK1, U/L | | 5.7 ± 7.8 | 2.6 ± 2.5 | 0.377 |

[1]E-S classification rubric as in ref. 23. [b]$P < 0.01$ and [a]$P < 0.05$, statistically significant; Statistics are presented as mean ± SD. AFP: α-fetoprotein; E-S: Edmondson-Steiner; HCC: Hepatocellular carcinoma; MVI: Microvascular invasion; TK1: Thymidine kinase-1.

Moreover, in this retrospective study, we further validated MVI as an independent prognostic factor correlated with HCC recurrence. A 50% HCC recurrence rate was found following surgical resection for tumors with MVI, despite antiviral therapy and chemotherapy. Thus, the possibility of recurrence for HCC with MVI is substantial. However, MVI can rarely be confirmed preoperatively and, consequently, it is difficult to choose an appropriate procedure (*e.g.*, wide resection margins) to prevent HCC recurrence[28]. Thus, it is important to identify preoperative imaging markers that could predict HCC recurrence.

It has been reported that conventional CT could be used to reconstruct global HCC gene expression patterns[29]. When Zhou *et al*[30] investigated the correlation between CT-based radiomics signature and early HCC recurrence, they identified internal arteries and necrosis as independent risk factors. Their results, which were similar to those of previous studies[5,29], led to their hypothesis that internal arteries may be correlated with MVI. The finding that necrosis is a marker of early HCC recurrence[30], however, is inconsistent with our study findings. We suspect that different follow-up times (1 year in their study *vs* 2 years in ours), was responsible for this difference.

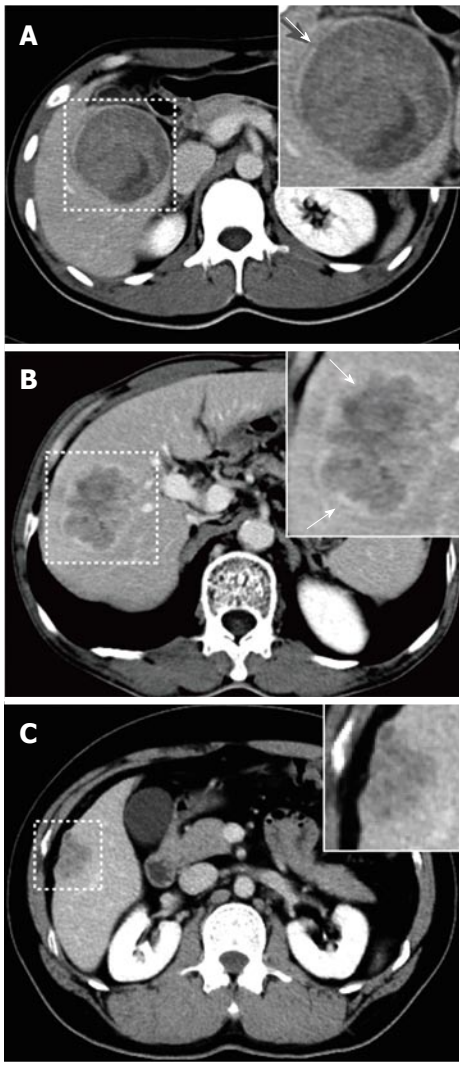


**Figure 2 Tumor capsules on the liver computed tomography map.** A: Equilibrium phase CT showing complete tumor capsule (red arrow) involvement at liver segment V in a 33-year-old male patient without postoperative recurrence (dashed box); B: Equilibrium phase CT showing incomplete tumor capsule (red arrow) at liver segments V and VI in a 57-year-old female patient with postoperative recurrence (dashed box); C: Equilibrium phase CT showing missing tumor capsule at liver segment VI in a 41-year-old male patient with postoperative recurrence (dashed box). CT: Computed tomography.

In this study, we further investigated whether preoperative CT findings correlate with HCC recurrence after surgical resection. Our finding that non-smooth tumor margins on CT could predict tumor recurrence has not been evaluated in previous studies. However, a previous study did show that non-smooth tumor margins on CT were predictive of MVI, and that MVI is an independent predictor of poor outcomes following surgical resection[13]. In our stratified analysis of tumors without MVI, tumor margins were significantly associated with postoperative recurrence during the follow-up period. This finding may be related to HCC multi-centricity being an important independent prognostic factor[31], and tumor aggressiveness should be considered[32]. We believe that non-smooth tumor margins can be considered an independent predictor of HCC recurrence.

Adachi *et al*[33] reported that vessels of the fibrous liver capsule were often invaded by tumor cells and that complete liver capsule fibrosis was a predictor of portal venous invasion. However, complete liver capsule fibrosis has been reported as a favorable prognostic marker because it can prevent HCC invasion into adjacent liver parenchyma[13]. Our results also showed that CT evidence of complete tumor capsules were associated with a low risk of postoperative recurrence. Peritumoral enhancement on magnetic resonance imaging (MRI) has been associated with a high risk of MVI[34]. In our study, peritumoral enhancement on CT was not related to HCC recurrence. The discrepancy in findings may be due to differences in imaging modalities used in various studies. Lu *et al*[35] reported that, when HCC was larger than 3 cm in diameter, the tumor tended to be more aggressive and was associated with a poor prognosis[36]. However, large tumor diameter was not a significant risk factor for postoperative recurrence in our study. At present, it is clear that HCC nodule size is not the only prognostic factor for recurrence[32]. Additionally, the relationship between postoperative HCC recurrence and AFP level remains controversial[5,10,11].

This study has two limitations. One potential limitation is the use of CT instead of MRI. Although CT is commonly used for HCC evaluation, MRI may provide additional information. A second limitation is the relatively small number of postoperative recurrences, except among those with preoperative evidence of MVI on CT. However, we further analyzed all cases and found similar results for the MVI-positive and MVI-negative groups. Thus, the study sample may reflect true population postoperative recurrences.

In conclusion, evaluation of patients with HCC should include preoperative CT findings of non-smooth tumor margins, incomplete tumor capsules and missing tumor capsules, which indicate possible postoperative recurrence. The treatment plan should include wide resection margins during curative resection, followed by antiviral therapy and chemotherapy.

## COMMENTS

### Background

Surgical resection of hepatocellular carcinoma (HCC) suffers from high rates of tumor recurrence. Although many potential risk factors for HCC postoperative recurrence have been described, a reliable preoperative method to estimate this risk has not been established. It has been reported that conventional computed tomography (CT) could be used to reconstruct global HCC gene expression patterns. Therefore, preoperative CT risk estimation for postoperative HCC recurrence should be clarified.

### Research frontiers

A reliable and validated prognostic method to estimate individual HCC recurrence risk would help guide future treatment strategies. The results of this study contribute to clarifying the correlation of CT signature with postoperative HCC recurrence.

### Innovations and breakthroughs

In the study, preoperative CT provides evidence of non-smooth tumor margins, incomplete tumor capsules and missing tumor capsules, which had been clarified as independent risk factors of postoperative HCC recurrence.

### Applications

This study suggests that preoperative CT is useful for predicting postoperative HCC recurrence. If the preoperative CT findings of a patient are non-smooth tumor margins, incomplete tumor capsules and missing tumor capsules, the treatment plan should include wide resection margins during curative resection, followed by antiviral therapy and chemotherapy.

### Peer-review

The manuscript from Zhang W *et al* reported the correlation of preoperative CT findings with postoperative HCC recurrence. HCC recurrence following curative resection may be predicted using CT. The entire sets of data are nicely presented, and highly supportive of the conclusion.

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