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Development and validation of a novel predictive scoring model for microvascular invasion in patients with hepatocellular carcinoma

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ABSTRACT

Purpose: Microvascular invasion (MVI) in patients with hepatocellular carcinoma (HCC) cannot be accurately predicted preoperatively. This study aimed to establish a predictive scoring model of MVI in solitary HCC patients without macroscopic vascular invasion.
Methods: A total of 309 consecutive HCC patients who underwent curative hepatectomy were divided into the derivation (n = 206) and validation cohort (n = 103). A predictive scoring model of MVI was established according to the valuable predictors in the derivation cohort based on multivariate logistic regression analysis. The performance of the predictive model was evaluated in the derivation and validation cohorts.
Results: Preoperative imaging features on CECT, such as intratumoral arteries, non-nodular type of HCC and absence of radiological tumor capsule were independent predictors for MVI. The predictive scoring model was established according to the β coefficients of the 3 predictors. Area under receiver operating characteristic (AUROC) of the predictive scoring model was 0.872 (95% CI, 0.817-0.928) and 0.856 (95% CI, 0.771-0.940) in the derivation and validation cohorts. The positive and negative predictive values were 76.5% and 88.0% in the derivation cohort and 74.4% and 88.3% in the validation cohort. The performance of the model was similar between the patients with tumor size ≤5 cm and >5 cm in AUROC ($P = 0.910$).
Conclusions: The predictive scoring model based on intratumoral arteries, non-nodular type of HCC, and absence of the radiological tumor capsule on preoperative CECT is of great value in the prediction of MVI regardless of tumor size.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor worldwide and the third most common cause of tumor-related deaths [1]. With the progression of surgical technology, curative resection and liver transplantation are now widely considered as the first choice of therapy for HCC. Unfortunately, the high postoperative recurrence of HCC remains a common problem. Approximately 70% of HCC patients have a recurrence within 5 years after curative hepatectomy [2].

Microvascular invasion (MVI), which is defined as the invasion of tumor cells in the intrahepatic portal vein or hepatic vein branches, is generally considered as a risk factor for the overall survival and recurrence rates of HCC patients after liver resection and transplantation [3]. Previous research reported that the incidence of MVI ranged from 15% to 57% in HCC specimens [4]. The presence of MVI is correlated with the aggressiveness of HCC [5]. Anatomical liver resection or local resection with a wide margin is recommended for initial treatment of HCC patients with MVI [6]. Currently, MVI is only confirmed after operation by histopathological diagnosis and surgeons cannot decide treatment strategy preoperatively according to MVI. Therefore, it is essential to predict the presence of MVI

Abbreviations: HCC, hepatocellular carcinoma; MVI, microvascular invasion; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; TB, total bilirubin; ALB, serum albumin; GGT, gamma glutamyl transpeptidase; AFP, alpha-fetoprotein; PLT, platelet count; CECT, contrast-enhanced computed tomography; SNEG, single nodule with extranodular growth; CMN, confluence multinodular; IG, infiltrative growth; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratios.

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preoperatively. Although many previous studies have tried to predict MVI, the sensitivity and specificity of each predictor are not high and these results need further validation in clinical research. Recently, with the development of radiological technology, some radiological features can be used to predict MVI. Gross classification of solitary HCC, peritumoral enhancement, radiological tumor capsule, and a typical dynamic enhancement pattern have been found to be helpful to predict MVI [7–10]. Furthermore, angiogenesis has been considered to be related to the invasiveness of HCC [11]. Numerous intratumoral vessels contribute to tumor cells migrating into the circulatory system. Segal et al. [12] found that the presence of intratumoral arteries on contrast-enhanced computed tomography was closely associated with the "venous invasion gene signature" of HCC, which promised to become an imaging marker for MVI. To our knowledge, there is limited research that comprehensively evaluated the predictive value of these imaging features and clinical characteristics.

In the present research, we retrospectively investigated imaging features and clinical characteristics of HCC patients, in order to establish a predictive scoring model according to the valuable predictors of MVI. Because MVI is more common in HCC patients with multiple lesions and advanced tumor stage, the research only selected solitary HCC patients without macroscopic vascular invasion, who are the main candidates for curative treatments.

2. Materials and methods

2.1. Study population

From January 2007 to March 2016, a total of 493 consecutive HCC patients underwent curative hepatectomy at Nanjing Drum Tower Hospital. To accurately establish a predictive scoring model, 184 patients were excluded for the following reasons: (1) macroscopic vascular invasion (n = 34), (2) multiple tumors (n = 45), (3) recurrent tumor (n = 39), (4) Child-Pugh C (n = 5), (5) R1 tumor resection (n = 4), (6) presence of any preoperative anticancer treatments (n = 30), (7) a history of other cancers (n = 6), and (8) incomplete clinical and imaging data (n = 21). We established the derivation cohort and the validation cohort from 2 different time periods. Patients enrolled from January 2007 to December 2014 were entered into the derivation cohort (n = 206). The remaining patients enrolled from January 2015 to March 2016 were entered into the validation cohort (n = 103). The present study was carried out in accordance with the Declaration of Helsinki, which was revised in 1983. The retrospective study was approved and exempted from the requirement to obtain informed consent by the Committee on Medical Ethics of Nanjing Drum Tower Hospital.

2.2. Clinical characteristics

Preoperative laboratory examinations and operation information were retrospectively reviewed from our HCC database, including age, gender, hepatitis B surface antigen (HBsAg), serum alanine aminotransferase (ALT), glutamyl-transpeptidase (GGT), serum total bilirubin (TB), serum albumin (ALB), alpha-fetoprotein (AFP), platelet count (PLT), Child-Pugh grade, background liver, tumor size, and type of surgery. Anatomical resection was characterized as any type of complete excision with at least 1 segment based on Couinaud's classification. Non-anatomical resection was defined as local resection or enucleation without regard to the Couinaud's segmental structure.

2.3. CT imaging protocol

All patients underwent contrast-enhanced computed tomography (CECT) using a multidetector CT scanner (LightSpeed VCT; GE Healthcare, Pittsburgh, PA, USA) with a 1.25-mm slice thickness. Parameters of the abdominal CT scan included a tube voltage of 120 kVp, tube current of 240 mA, rotation time of 0.6s, helical pitch of 1.375, field of view of 35–40 cm and matrix of 512 × 512. For the triphasic protocol, hepatic arterial, portal venous and equilibrium phase images were obtained 30, 60 and 180 s after the injection of contrast media (Omnipaque 350 mg I/mL; GE Healthcare) at a rate of 3.0 mL/s with a dose of 1.5 mL/kg bodyweight. All patients underwent CECT within 1 month before surgery.

2.4. Image analysis

All CT images were independently evaluated by 2 experienced radiologists (H.J. and T.M.), who were blinded to the clinical and histopathological information. Any discrepancies between the 2 radiologists were resolved by discussion to reach consensus. In each HCC patient, intratumoral arteries, gross classification of HCC, peritumoral enhancement, radiological tumor capsule and typical dynamic enhancement pattern were evaluated and recorded. Intratumoral arteries were defined as the discontinuous and tortuous arterial enhancement in tumors in arterial and/or portal venous phases (Fig. 1**A**) [13]. The radiological tumor capsule was defined as a thin, complete and enhanced rim around the tumor in the portal venous and/or equilibrium phases (Fig. 1**B**) [9]. An incomplete ring and corona enhancement around the tumor was not included. Peritumoral enhancement was defined as the presence of an irregular enhancement region in the arterial phase, adjacent to the tumor margin, that then became isodense compared with the background liver parenchyma in the equilibrium phase (Fig. 1**C**) [4]. Wedge-shaped peritumoral enhancement was not included. Typical dynamic enhancement pattern was defined as arterial hyperenhancement followed by washout in portal venous and/or equilibrium phases (Fig. 1**D**) [14]. Gross classification of HCC was divided into single nodule (SN) and non-nodule types based on the outline of the tumor in the portal venous and equilibrium phases. Based on our previous research [15], SN type was defined as the single nodule that had a round or oval shape with a clear boundary. Non-nodule type was defined as a single nodule with extranodular growth (SNEG), confluence multinodular appearance (CMN), and infiltrative growth (IG) type (Fig. 2). All CT images were evaluated in axial, coronal, and sagittal planes.

2.5. Histopathological characteristics

All of the resected specimens were cut into approximately 3- to 5- mm thick slices and fixed in 1% formalin for further pathological examination. The liver slices were embedded in paraffin, cut into 4-mm sections, and stained with hematoxylin and eosin. At least a slice of normal liver parenchyma 1 cm away from the tumor edge was examined. We correlated pathological specimens with imaging characteristics. Intratumoral arteries were associated with many abnormal disorderly blood vessels in the specimen section (Supplementary Fig. 1). Tumor capsule was defined as the fibrous capsule enveloping the tumor microscopically, and consisted of the fibrous component, small vessels and/or a little liver parenchyma (Supplementary Fig. 2). The gross classification of the resected specimen was based on previous research [15,16]. All of the cases were divided into SN type and non-nodule type. Non-nodule type included single nodule with extranodular growth, confluence multinodular appearance and infiltrative growth type (Supplementary Fig. 3). The extent of tumor differentiation was evaluated as well, moderate, and poor according to the Edmondson-Steiner grading system [17]. MVI was defined as the invasion of tumor cells in a portal vein, hepatic vein, or a large capsular vessel of the surrounding hepatic tissue, partially or totally lined by endothelial cells that was visible only on microscopy [18]. All of