Prognostic CT Features and Prediction Model of Patients With Primary Hepatocellular Carcinomas Undergoing Partial Hepatectomy

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary malignant tumor in the liver. Partial hepatectomy is one of the most effective therapies for HCC but suffer from the high recurrence rate. At present, the studies of association between clinical outcomes and CT features of patients with HCCs undergoing partial hepatectomy are still limited. The purpose of this study is to determine the predictive CT features and establish a model for predicting relapse or metastasis in patients with primary hepatocellular carcinomas (HCCs) undergoing partial hepatectomy.

Methods: The clinical data and CT features of 112 patients with histopathologically confirmed primary HCCs were retrospectively reviewed. The clinical outcomes were categorized into two groups according to whether relapse or metastasis occurred within 2 years after partial hepatectomy. The association between clinical outcomes and CT features including tumour size, margin, shape, vascular invasion (VI), arterial phase hyperenhancement, washout appearance, capsule appearance, satellite lesion, involvement segment, cirrhosis, peritumoral enhancement and necrosis was analyzed using univariate analysis and binary logistic regression. Then establish logistic regression model, followed by receiver operating characteristic (ROC) curve analysis.

Results: CT features including tumor size, margin, shape, VI, washout appearance, satellite lesion, involvement segment, peritumoral enhancement and necrosis were associated with clinical outcomes, as determined by univariate analysis (P<0.05). Only tumor margin and VI remained independent risk factors in binary logistic regression analysis (OR=6.41 and 10.92 respectively). The logistic regression model was logit(p)=-1.55+1.86 margin +2.39 VI. ROC curve analysis showed that the area under curve of the obtained logistic regression model was 0.887(95% CI 0.827-0.947).

Conclusion: Patients with ill-defined margin or VI of HCCs were independent risk predictors of poor clinical outcome after partial hepatectomy. The model as logit(p)= -1.55+1.86 margin +2.39 VI was a good predictor of the clinical outcomes.

1. Background

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor in the liver. HCC is the fourth most common cause of cancer-related death worldwide [1]. Partial hepatectomy is one of the most effective therapies for HCC, but the recurrence rate is as high as 60%-70% [2]. At present, computed tomography (CT) is the most common imaging modality for HCC diagnosis in China. The imaging findings of HCC have been extensively described [3–9]. Previous studies have found that poor survival of patients with HCCs is associated with clinical and histological factors concluding tumor size >5 cm, presence of satellite lesions, vascular invasion, KIF3B expression [10–12]. Recently, some studies have reported that gross vascular invasion, irregular tumour margin and peripheral ragged enhancement, location in the liver, and nodule size on CT/MRI for HCC undergoing chemoembolization were independently associated with overall survival [13, 14]. To date, the reports of association between

clinical outcomes and CT features of patients with HCCs undergoing partial hepatectomy are limited [15, 16]. Hence, more prognostic CT features of patients with HCCs undergoing partial hepatectomy should be assessed, and prediction model should be established to predict the clinical outcome. In this study, we retrospectively reviewed various CT findings in a series of 112 patients with partial hepatectomy and pathologically proved HCCs, and used logistic regression analysis to identify the predictive CT features and set up a prediction model for predicting relapse or metastasis in these patients.

2. Materials And Methods

2.1 Patients

Between June 2007 and March 2016, 112 patients with pathologically confirmed primary hepatocellular carcinomas of our hospital were enrolled in this retrospective study. Patients were included if they had a pathologically confirmed HCC, partial hepatectomy, primary lesion in liver without extrahepatic metastasis, and abdomen CT examination before treatment. This study was approved by the Institutional Review Board of the University of Hong Kong-Shenzhen Hospital, and patient informed consent was waived for this type of review.

Clinical data including clinical outcome, presentation, age, sex and treatment were reviewed. Medical records of all patients were well maintained. The patients were follow-up of 3 to 92 months (mean 33.4 months). Sixty-seven patients had local relapse or metastases within 2 years after surgery, and forty-six patients survived without any evidence of relapse or metastasis at least 2 years after therapy. There were 88 males and 34 females, aged from 19 years to 81 years with a mean of 52.3 years. The main symptoms were weight loss (n =59), abdominal pain (n=35), fatigue (n =25) and jaundice (n=14). Nine patients were detected during a regular medical checkup. All patients were treated with hepatic resection. After surgery, tumor specimens were processed for histologic examination.

2.2 CT imaging

All patients had abdomen CT imaging before surgery. CT imaging in 64 patients was performed using a 64-slice spiral CT (LightSpeed VCT, GE Medical Systems, Milwaukee, WI, USA), and in the remaining 48 patients using a 4-slice spiral CT (Somatom volume zoom; Siemens Medical Systems, Erlangen, Germany). The imaging parameters included a tube voltage of 120 kV, 300-350 effective mAs, a field of view of 380 mm, a pitch of 0.9-1.2, and a matrix of 512×512. Axial, sagittal and coronal multiplanar reconstructions (MPR) images with 2–5 mm thick were obtained with soft tissue kernels. After acquisition of unenhanced images, triphasic contrast-enhanced CT imaging was obtained after intravenous injection of contrast media (Iopamiro 370; Bracco S.P.A., Milan, Italy) through a dual-head injector at flow rate of 3.5 ml/s and followed by 20-mL saline flush, with a dosage of 1.2 ml/kg of body weight. A bolus-tracking technique was used to determine the timing for the hepatic arterial phase (HAP) scanning, with a region of interest in the descending aorta. After achieving enhancement of the descending aorta up to 100 HU, the HAP images were acquired with the scanning delay of 5 s. Portal venous phase (PVP) images and equilibrium phase were obtained with a delayed time of 30 s and 120 s,

respectively. When the 4-slice spiral CT was used, CT scans were obtained at 30 sec (HAP) and at 60 sec (PVP) after intravenous injection of contrast media.

2.3 Imaging analysis

CT scan data were reviewed on PACS system for all patients by two experienced radiologists in consensus (C.Z. with more than 13 years of experience with diagnostic imaging, and X.D. with 10 years of experience with diagnostic imaging). CT imaging features including primary tumour size, margin, shape, vascular invasion (VI), arterial phase hyperenhancement, washout appearance, capsule appearance, satellite lesion, involvement segment, cirrhosis, peritumoral enhancement and necrosis. Tumor size was measured in maximal dimension on the transverse plane. The margin of the lesion was considered as well-defined or ill-defined. The shape of the lesion was classified as irregular or regular. The regular shape was defined as round/ovoid, and irregular was lobulated. VI defined as if lesion invaded hepatic vein or portal vein. Washout appearance was defined as a visually assessed reduction in enhancement relative to surrounding liver in PVP. Density of the lesion was classified as hypodensity, isodensity or hyperdensity compared with liver on unenhanced CT image. Involvement segment classified as single or multiple. Peritumoral enhancement was defined as peritumoral enhancement in the HAP or PVP was greater than that of surrounding liver. The degree of tumor necrosis was categorized as absent, mild (<50% necrosis of the tumor), and severe (>50% necrosis of the tumor) in contrast-enhanced PVP CT scan.

2.4 Statistical analysis

To determine the prognostic value of the CT features, the clinical outcomes of patients were categories into two groups: poor outcome if relapse or metastases occurred within 2 years after partial hepatectomy; good outcome if patients survived for more than 2 years with no evidence of relapse or metastasis after partial hepatectomy. The CT imaging features included for analysis were categorized as follows: lesion size (>5cm or ≤5 cm),[10,12] margin (ill-defined or well-defined), shape (irregular or regular), VI (presence or absence), arterial phase hyperenhancement (presence or absence), washout appearance (presence or absence), capsule appearance (presence or absence), satellite lesion (presence or absence), involvement segment (single or multiple), cirrhosis (presence or absence), peritumoral enhancement (presence or absence) and necrosis (absence, mild or severe). Univariate analysis was applied to compare the frequency of these imaging findings between good and poor outcome groups by using χ^2 test. Variables with *P* value less than 0.05 as determined by univariate analysis were subsequently used binary logistic regression analysis to determine association between the clinical outcomes and CT features. Variables with P value less than 0.05 as determined by the logistic regression analysis were chosen as the independent predictor for clinical outcomes, Odds ratios (OR) as estimates of relative risk with 95% confidence intervals (CI) were obtained for each risk factor. A two-side *P* value of less than 0.05 was considered statistically significant. Then, establish logistic regression model of patients with HCCs. Furthermore, receiver operating curve (ROC) analysis was used to evaluate the obtained logistic regression model. All statistical tests were performed by using software (SPSS, version 22.0, Chicago, IL, USA).

3. Results

3.1 Imaging features

The main CT characteristics of 112 patients are summarized in Table 1. The size of the lesions ranged from 1.1 to 11.2 cm, with a mean of 5.90 cm. Lesions were irregular in 68 patients (60.7%) (Figs. 1, 2), while regular in other 44 patients (39.3%) (Fig. 3). Ill-defined margin of lesions was found (Figs. 1, 2) in 55 patients (49.1%) and well-defined (Fig. 3) in the remaining 57 patients (50.9%). VI of HCCs was found in 28 patients (Fig. 1, 2). Arterial phase hyperenhancement (Fig. 2, 3) was found in 82 patients (73.2%), washout appearance (Fig. 1, 2) was found in 104 (92.9%), and the combination of them was found in 74 (66.07%). Capsule appearance was found in 47 patients (42.0%, Fig. 3)). Satellite lesion was found in 17 patients (15.2%). Lesion involved single segment was found in 53 patients (47.3%), and involved multiple segments in the other 59 patients (52.7%). Primary lesions showed isodensity in 1 patient, hypodensity in 104 patients and hyperdensity in 7 patients on unenhanced CT images. Tumor internal fat density was found in 1 patient.

Table 1
CT features of 112 patients with primary hepatocellular carcinoma

Characteristics	No. of patients	%
Tumor size (cm)*	5.90±3.14 (range,1.1-16.2)	
Tumor margin		
Well-defined	57	50.9
Ill-defined	55	49.1
Tumor shape		
Irregular	68	60.7
Regular	44	39.3
Necrosis		
Absent	28	25.0
Mild	71	63.4
Severe	13	11.6
Vascular invasion		
Present	28	25.0
Absent	84	75.0
Arterial phase hyperenhancement		
Present	82	73.2
Absent	30	26.8
Washout appearance		
Present	104	92.9
Absent	8	7.1
Capsule appearance		
Present	47	42.0
Absent	65	58.0
Satellite lesion		

*Mean±SD;

Characteristics	No. of patients	%
Present	17	15.2
Absent	95	84.8
Involvement segment		
Multiple	59	52.7
Single	53	47.3
Cirrhosis		
Present	70	62.5
Absent	42	37.5
Peritumoral enhancement		
Present	40	35.7
Absent	72	62.3
*Mean±SD;		

Table 2
Univariate analyses of CT factors

Factor	Category	No. of poor outcome vs. good outcome
Tumor size	≥5.0cm	45:15*
	<5.0cm	21:31
Tumor margin	Ill-defined	49:6**
	Well-defined	17:40
Tumor shape	Irregular	53:15**
	Regular	13:31
Vascular invasion	Presence	27:1**
	Absence	39:45
Arterial phase hyperenhancement	Presence	50:32
	Absence	16:14
Washout appearance	Presence	65:39*
	Absence	1:7
Capsule appearance	Presence	28:19
	Absence	38:27
Involvement segment	Multiple	42:17*
	Single	24:29
Cirrhosis	Presence	44:26
	Absence	22:20
Peritumoral enhancement	Presence	32:8*
	Absence	34:38
Necrosis	Severe	12:1*
	Mild	43:28
	Absence	11:17

*P<0.05; ** P<0.01

3.2 Predictive value of imaging features

Sixty-six patients (58.93 %) had local relapse or metastases within 2 years after partial hepatectomy, and were categorized as the poor outcome group. Forty-six patients (41.07 %) survived without any evidence

of relapse or metastasis at least 2 years after partial hepatectomy, and were classified as the good outcome group. CT features including tumor size, margin, shape, VI, washout appearance, satellite lesion, involvement segment, peritumoral enhancement and necrosis were associated with clinical outcome, as determined by univariate analysis (P<0.05) (Table 2). In logistic regression analysis, only tumor margin and VI of the primary HCC remained significantly independent predictors of clinical outcome (P<0.05) (Table 3). The patients with ill-defined margin or VI of HCCs were likely to have poorer outcome than those with well-defined margin or without VI (OR=6.41 and 10.92 respectively). The logistic regression model was logit(p)= -1.55+1.86 margin +2.39 VI. Further ROC curve analysis showed that the area under curve (AUC) of the obtained logistic regression model was 0.887 (95% CI: 0.827-0.947), which indicated that the logistic regression model was a good predictor of the clinical outcomes (Fig. 4).

Table 3
Binary regression analysis of various CT factors

Factors	Category	β value	*P* value	OR (95% CI)
Tumor size	≥5.0cm	0.001	0.999	1.00 (0.29, 3.46)
Tumor margin	Ill-defined	1.86	0.002	6.41(1.93, 21.31)
Tumor shape	Irregular	0.64	0.302	1.89 (0.56, 6.35)
Vascular invasion	Presence	2.39	0.032	10.92(1.23,97.17)
Washout appearance	Presence	1.41	0.258	4.11(0.35,47.69)
Satellite lesion	Presence	0.50	0.575	1.65(0.29, 9.35)
Involvement segment	Multiple	-0.01	0.980	0.97(0.32,3.02)
Peritumoral enhancement	Presence	0.50	0.436	1.65(0.47,5.76)
Necrosis	Severe	-1.14	0.372	0.32(0.03,3.94)
	Mild	-1.32	0.274	0.27(0.03,2.85)

4. Discussion

HCC is a major health problem worldwide. Chronic infection by the hepatitis B virus is the most common cause of this disease. The peak age of incidence is 50–70 years, with a male predominance [12, 16]. There are several treatment strategies available for HCC. Resection is the first-line of therapy in patients with HCCs and well-preserved liver function. However, the recurrence rate after surgery is high [2, 12]. In our study, the recurrence or metastases rate was 58.93% within 2 years after surgery. HCC recurrence after hepatic resection is divided into early recurrence (within 1 or 2 years after surgery) and late recurrence (greater than these temporal end-points) [17,18]. Early recurrences are considered to result from metastasis of the primary HCC and are mainly affected by adverse tumor features, whereas late recurrences should be considered as de novo HCCs and are mainly affected by the underlying liver

status [17,18]. In this study, we retrospectively reviewed various CT findings of 112 patients with primary HCCs to assess the association between CT features and early clinical outcome after surgery.

Multiphasic helical CT is often used as the first-line diagnostic modality for detection of HCC. The sensitivity of CT for HCC of all size is 63%-76% [6]. The accuracy of CT in the diagnosis of HCC was 94.29%, and that of lesion with a diameter ≤1 cm was 84.00% [5]. Hepatic artery is the primary feeder to the HCC. The hallmark diagnostic CT features of HCC are arterial phase hyperenhancement followed by portal venous or delayed phase washout appearance [3-6]. The arterial phase hyperenhancement is characteristic but nonspecific to radiological diagnosis of HCC, as it can also be observed in focal nodular hyperplasia, hemangiomas, hypervascular metastases and hepatic adenoma. While the combination of arterial phase hyperenhancement and washout appearance is highly specific for HCC in patients with risk factors for HCC [19, 20]. In our series, the combination of them was found in 66.07% patients. Capsule appearance is another important imaging feature for HCC, and is observed in about 42% of cases [19]. Consistently, in our study, capsule appearance was found in 47 patients (42.0%). According to the diagnostic systems [21], a mass 2 cm or larger with arterial phase hyperenhancement and capsule appearance can be diagnosed definitively as HCC even in the absence of washout appearance; for 10- to 19- mm masses with arterial phase hyperenhancement, both capsule appearance and washout appearance are required.

Previously, many factors concluding tumor size >5 cm, presence satellite lesions, vascular invasion, KIF3B expression, α-fetoprotein level have been described as important prognostic factors for poor clinical outcome [10-12, 22], but tumor capsule has been described as a protect effect for clinical outcome [12]. Other than these clinical and histological factors, Baek et al. reported that increased 18F-FDG uptake of HCCs, especially high tumor-to-muscle might be correlated with microvascular invasion and poor differentiation, and tends to have a risk for recurrence in HCC [23]. Kitao et al. reported that hypervascular HCCs that hyperintensity relative to the surrounding liver on hepatobiliary phase gadoxetic acid-enhanced MR images demonstrate a significantly higher grade of differentiation, rarer portal vein invasion and lower recurrence rate than those of hypointense HCCs [24]. In addition, Honda et al. reported that the combination of normal hepatic arterial degeneration and preserved portal veins results in low attenuation on CT arteriography and isoattenuation on CT arterioportography in well differentiated lesions, and the combination of neoplastic (abnormal) arterial development by angiogenesis and obliteration of portal veins results in high attenuation on CT arteriography and low attenuation on CT arterioportography in advanced HCC [25].

Recently, some studies have reported that gross vascular invasion, irregular tumour margin and peripheral ragged enhancement, location in the liver and nodule size on CT/MRI for HCC undergoing chemoembolization were independently associated with poor overall survival [13, 14]. Moreover, there is reported that lobular configurations on CT was important independent factor for long-term survival after resection [15]. Li et al. reported that corona enhancement on CT for patients with a single HCC>5cm without extrahepatic metastasis was a significant factor for overall survival [16]. As more prognostic CT features of patients with HCCs undergoing hepatic resection are need to determined, we reviewed various

CT findings including tumour size, margin, shape, VI, arterial phase hyperenhancement, washout appearance, capsule appearance, satellite lesion, involvement segment, cirrhosis, peritumoral enhancement and necrosis, and used logistic regression analysis to identify the predictive CT features and set up a prediction model. Univariate analysis showed that CT features including tumor size, margin, shape, VI, washout appearance, satellite lesion, involvement segment, peritumoral enhancement and necrosis were associated with clinical outcome, but only tumor margin and VI of the primary HCC remained independent predictors of clinical outcome in logistic regression analysis. Hence, patients with ill-defined HCCs were more likely to have local relapse or metastases within 2 years after surgery than those with well-defined HCCs, with OR of 6.41. Meanwhile, patients with VI of HCCs were more likely to have local relapse or metastases within 2 years after surgery than those without VI, with OR of 10.92. The logistic regression model was logit(p)= -1.55+1.86 margin +2.39 VI. Further ROC curve analysis showed that the area under curve (AUC) of the obtained logistic regression model was 0.887(95% CI 0.827-0.947)., which indicated that the prediction model was a good predictor of the clinical outcomes.

There were several limitations in our study. First, as a large number of patients are needed for logistic regression analysis, we enrolled patients using 4 or 64-slice spiral CT. Second, no state-of-art CT was used in our study, which might represent more valuable parameters for HCC. It is well known that dual-energy CT is an excellent qualitative as well as a quantitative tool for assessing and predicting hepatocellular carcinoma [26,27]. Further prospective study using state-of-art CT may provide additional information of radiologic risk predictors.

Conclusions

In conclusion, our study results suggest that tumor margin and VI of the primary HCC are independent risk factor for the clinical outcome after partial hepatectomy. The model as logit(p)= -1.55+1.86 margin +2.39 VI was a good predictor of the clinical outcomes after partial hepatectomy.

Abbreviations

HCC: Hepatocellular carcinoma; CT: Computed tomography; MPR: Multiplanar reconstructions; HAP: Hepatic arterial phase; PVP: Portal venous phase; VI: Vascular invasion; ROC: Receiver operating curve; OR: Odds ratios; CI: Confidence intervals.

Declarations

Acknowledgement

Not applicable.

Authors' contributions

C.Z. and X.B.: conceptualization and design, visualization, methodology, writing- original draft preparation. H.H., Q.Y., R.Z., C.X. L.Y.: methodology, validation, data curation, formal analysis, investigation. X.S., X.D.: conceptualization and design, methodology, writing- review & editing. All authors read and approved the final manuscript. C.Z. and X.B. contributed equally to this work.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the University of Hong Kong-Shenzhen Hospital, and patient informed consent was waived for this type of review. The methods in this study were carried out in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

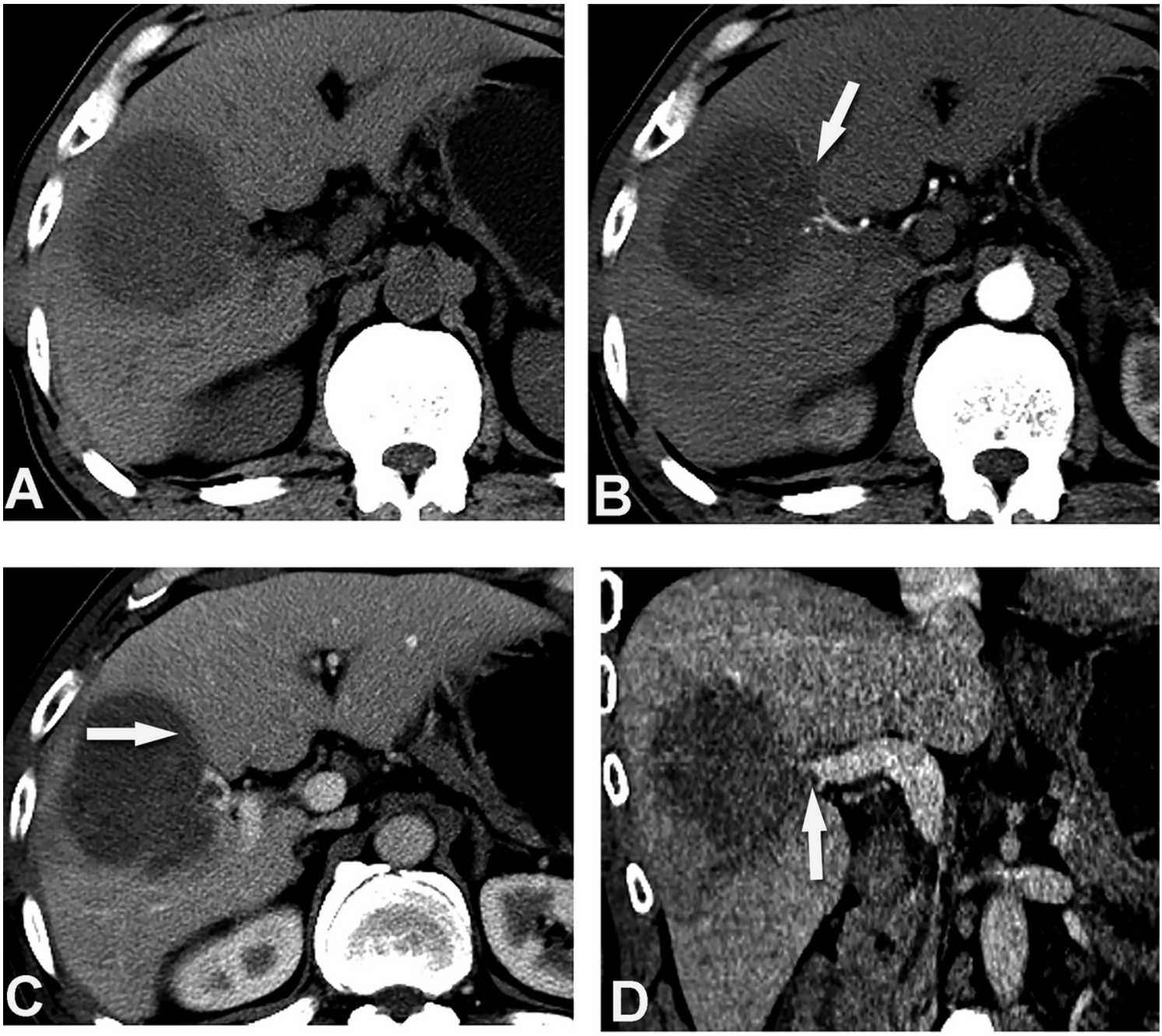

Figure 1

A 47-year-old man with HCC had relapse 6 months after partial hepatectomy. Axial non-contrast CT image (A) shows a hypodense and irregular mass in the liver. Arterial phase contrast-enhanced CT image (B) shows enlarged vessels feeding or drain the mass (arrow). Axial (C) and coronal (D) portal venous phase contrast-enhanced CT images show a mass with ill-defined margin, washout appearance and vascular invasion (arrow).

Figure 2

A 50-year-old man with HCC had relapse 6 months after partial hepatectomy. Axial non-contrast CT image (A), arterial phase contrast-enhanced CT image (B) and portal venous phase contrast-enhanced CT image (C) shows an ill-defined, irregular mass in the segment Ⅶ and Ⅷ of the liver. The tumour shows hypodensity on non-contrast CT image, enlarged vessels feeding or drain the mass (arrow) and heterogeneously hyperenhancement on arterial phase contrast-enhanced CT image, washout appearance, vascular invasion (arrow) and mild necrosis on portal venous phase contrast-enhanced CT image.

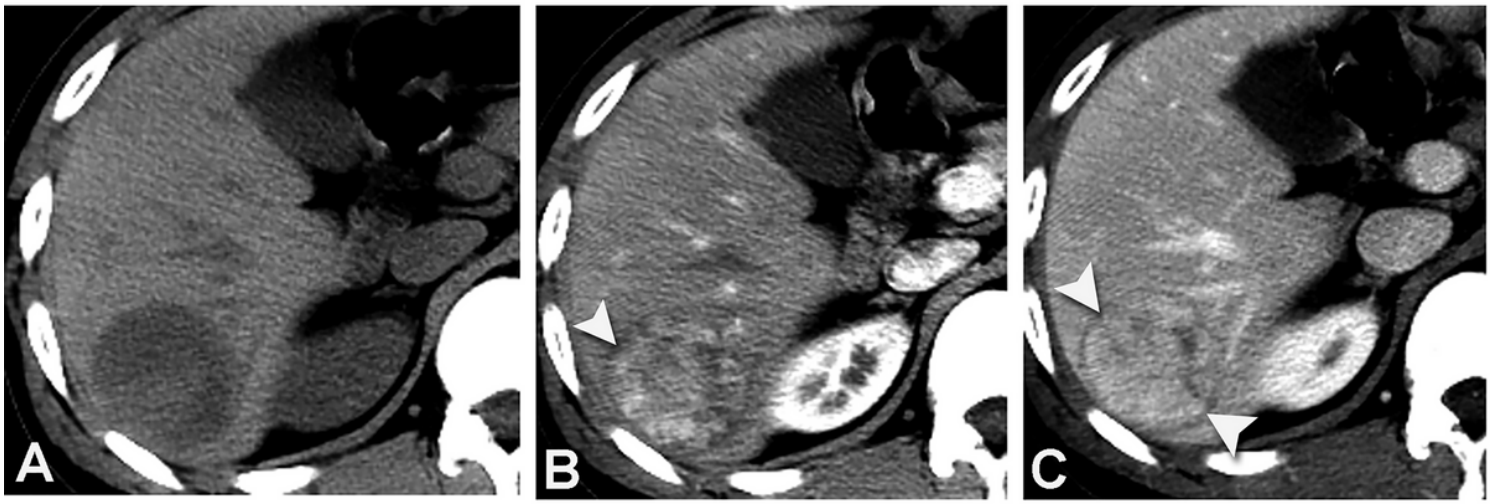

Figure 3

A 50-year-old man with HCC survived for 4 years after surgery without any evidence of relapse or metastasis. Axial non-contrast CT image (A), arterial phase contrast-enhanced CT image (B) and portal venous phase contrast-enhanced CT image (C) show a well-defined, regular mass with capsule appearance (arrow head) in the segment Ⅶ of the liver. The tumour shows hypodensity on non-contrast CT image, heterogeneously hyperenhancement on arterial phase contrast-enhanced CT image and no washout appearance on portal venous phase contrast-enhanced CT image.

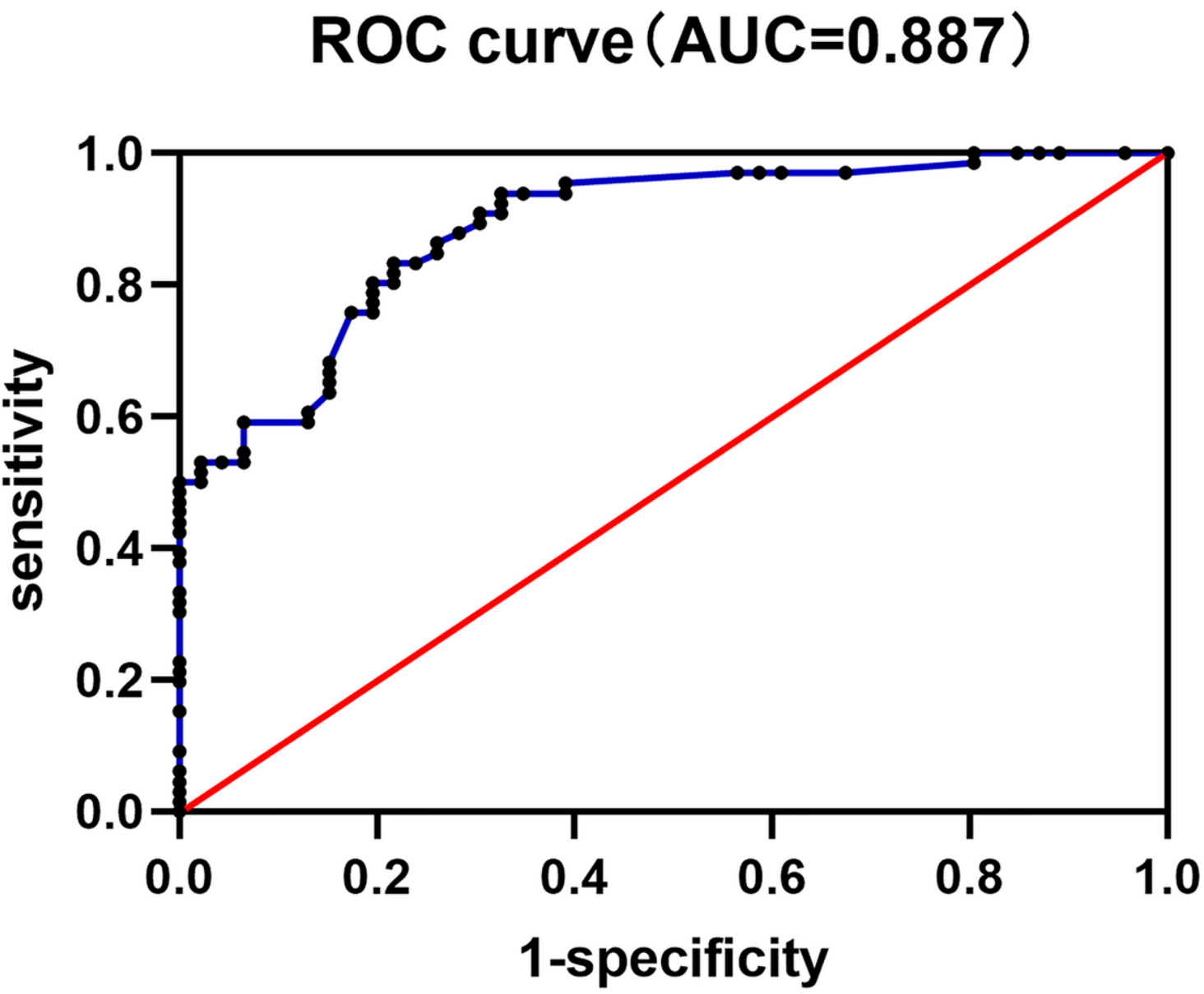

Figure 4

Graph shows the receiver operating characteristic (ROC) curve of the logistic regression model. The area under the curve (AUC) was 0.887.