Title: Evaluation of hepatocellular carcinoma spread via the portal system by 3-dimensional mapping

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Disclosure/conflict of interest

The authors declare that there are no conflicts of interest.

Abstract

Background/Purpose: The pattern of tumor cell spread via the portal system has not been fully clarified in patients with hepatocellular carcinoma (HCC). This study aimed to evaluate the intrahepatic distribution of cancer cells derived from the main tumor by assessing histological portal invasion and/or intrahepatic metastasis (vp/im) .

Methods: In 14 patients who underwent anatomical resection of primary solitary HCC ≤ 50 mm in diameter, vp/im were examined pathologically, and the sites of the lesions were reproduced on preoperative 3D-CT images. The number of vp/im and the distance of each lesion from the tumor margin were also determined.

Results: The tumor diameter was < 30 mm in seven patients (smaller HCCs) and 30-50 mm in seven patients (larger HCCs). 3D mapping revealed that almost all vp/im were localized to the peritumoral area within one cm of the tumor margin in smaller HCCs, whereas vp/im seemed to spread extensively to the feeding 3rd level portal branches in larger HCCs. The number of vp/im was greater in patients with larger HCCs than in those with smaller HCCs.

Conclusions: 3D mapping suggested tumor cells of HCC spread via the portal vein extensively in several cases.

Main Text

Introduction

Hepatic resection is a widely accepted treatment for hepatocellular carcinoma (HCC), but it is often difficult to determine the optimal extent of resection due to the presence of underlying liver disease such as chronic hepatitis or cirrhosis［1-3］. The most important factors related to a poor prognosis of HCC are reported to be tumor size, microvascular invasion of the portal vein (*vp*), and intrahepatic metastasis (*im*)［4-6］. In addition, it is well known that the portal vein is an efferent vessel for HCC ［7］ and "*im*" can occur by "*vp*" ［8-12］. Therefore, anatomical resection based on the portal territory is theoretically seemed to be preferable to non-anatomical resection for reducing postoperative intrahepatic recurrence. Although there have been several reports that HCC with *vp* and/or *im* (*vp/im*) shows early recurrence after resection［13-19］, the pattern and extent of tumor cell spread via the portal system have not been fully clarified, so the optimal extent of resection is still controversial. To evaluate the optimum extent of resection for HCC, the distribution of microscopic *vp/im* was assessed by 3-dimensional computed tomography (3D-CT) mapping.

Materials and Methods

Patients

Institutional ethics committee approval and informed consent were obtained for this study. The inclusion criteria were as follows: (i) patients with primary solitary HCC, (ii) tumor ≤50 mm in diameter, (iii) no preoperative treatment, (iv) no preoperative portal vein embolization (PVE) for hypertrophy of the future liver remnant, (v) curative resection with an adequate margin, and (vi) a histological diagnosis of HCC. From January 2015 to March 2016, a total of 113 patients who underwent resection of HCC at our institution were considered for inclusion in this study. Among these 113 patients, 56 met the inclusion criteria (25 patients were excluded for recurrent tumor, seven for multiple tumors, eight for tumor size more than 5 cm, eight for preoperative treatment, six for a history of PVE and three for inadequate margins). Of these 56 patients, 26 patients (46%) revealed a histological evidence of *vp/im*. Twelve of 26 patients with *vp/im* underwent non-anatomical resection. They were excluded from analysis because the relation between *vp/im* lesions and portal vein in the resected specimens could not be evaluated adequately. Therefore, the remaining 14 of 56 patients (25%) were

investigated using resected specimens (Fig. 1). Anatomical resection was defined as lobectomy, central bisegmentectomy, or segmentectomy, while non-anatomical resection was defined as resection not conforming to segmental, sectional, or lobar anatomy.

Preparation for 3D mapping

In all 14 patients, fresh resected liver specimens were fixed in 10% buffered formalin, and serial slices about 5 mm thick were cut in the axial plane. Each slice was divided into several tissue blocks that were placed into Path Cassettes® labeled with the slice number and sequential tissue block number. All tissue blocks were further fixed in 10% buffered formalin, embedded in paraffin, cut into 4-μm sections, and stained with hematoxylin and eosin. The existence of *vp/im* was examined in all areas of the resected specimens and histological *vp/im* lesions were marked on the glass slides, and were subsequently reproduced on preoperative multi-detector CT (MD-CT) images with the axial plane on MD-CT images corresponding to the view of the intrahepatic vessels on the glass slides. Finally, 3D reconstruction of images was done using a work station

(SYNAPSE VINCENT®) (Fig. 2). In addition, the *vp/im* lesions were counted and the distance of each lesion measured from the border of the main tumor with a ruler to assess the extent of tumor spread. In this study, "*im*" was defined as a nodule that was histologically similar to or less differentiated than the main tumor［20. 21］, while "*vp*" was defined as histological portal vein tumor thrombus in the liver parenchyma. Because "*vp*" and "*im*" were often impossible to distinguish microscopically, both "*vp*" and "*im*" were investigated as portal tumor spread in this study since "*im*" should originate from "*vp*". However, it was also difficult to distinguish metastasis from multicentric carcinogenesis in several lesions. Therefore, multicentric tumors were defined as nodules that contain well-differentiated cells［20］and were excluded from analysis.

Results

The demographic details of the 14 studied patients are provided in table 1. All were classified as Child-Pugh score 5 and class A.

Frequency of *vp/im*

Among 56 patients with resected HCC, 26 patients (46%) showed several histological *vp/im* in this study (Fig.1). According to tumor size, 15 of 44 patients (34%) with tumors less than 30 mm revealed *vp/im*, while no less than 11 of 12 patients (91%) with tumors 30-50 mm showed *vp/im* (data not shown).

Number and location of *vp/im*

Table 2 showed the tumor size and histological findings in each patient. A total of 321 sites of *vp/im* were found in 1528 slides prepared from the resected specimens of the 14 patients, with *vp/im* being more frequent in larger HCCs than in smaller HCCs (195 vs. 126). Among the smaller HCCs, only 1 of 126 *vp/im* lesions (0.7%) was located over 1 cm from the tumor margin, while 20 of 195 lesions (10.2%) were over 1 cm from the margin in larger HCCs. Furthermore, four of the 195 lesions (2.0%) in larger HCCs were located over 2 cm from the main tumor *versus* no lesions in smaller HCCs (Fig. 3).

3D mapping of smaller HCCs

Figure 4 (A, B: case 2, C-E: case 5) shows representative 3D mapping images of

smaller HCCs. Almost all *vp/im* were located within 1 cm of the tumor margin in the patients with smaller HCCs (Fig. 4B, D). However, case 5 had a tumor 20 mm in size of the confluent multinodular type macroscopically, consecutive micro-tumor thrombosis was detected at 11mm from the main tumor in the proximal area toward the hepatic hilum (Fig. 4E: black arrow).

3D mapping of larger HCCs

Figure 5 shows 2 representative cases (A, B: case 10, C, D: case 11), in which *vp/im* seemed to spread as far as the feeding 3rd order portal venous branches of the tumor (Fig. 5B, D; arrow). Both of these patients had tumors over 40 mm in size. In case 11, HCC was infiltrative with sarcomatous change histologically, and the most distant *vp/im* in this series was detected at 4 cm from the tumor margin (Fig. 5D; circle).

Discussion

Hepatic resection is widely accepted as the most curative treatment for HCC, but the most important problem is prevention of postoperative recurrence to achieve a better

prognosis. It has been reported that the portal vein can act as an efferent vessel of HCC ［7］. A histological study has suggested that the main drainage vessels of hepatocellular nodules change from hepatic veins to hepatic sinusoids and then to portal veins during the multi-step process of hepatocarcinogenesis［22, 23］. In addition, it has been suggested that the portal vein invasion around the main tumor causes intrahepatic spread via the portal system and formation of secondary nodules［24］. With respect to preventing the spread of cancer via the portal system, complete removal of the portal segment containing the tumor is generally recommended to eradicate intrahepatic metastasis. However, it is uncertain whether anatomical resection actually eradicates all of the malignant cells derived from the main tumor. Therefore, we investigated the distribution of *vp/im* in resected liver specimens and also performed 3D-CT imaging of *vp/im* in order to assess the spread of HCC in this study.

The mode of tumor cells spread is still unclear. It has been suggested that malignant cells spread radially in all directions from the main tumor［25］, but some authors have claimed that tumor cells spread via the portal territories［8-12, 26, 27］. Other investigators have identified malignant cells from the main tumor not only in distal

regions, but also proximal to the hilum which is against the direction of portal flow ［28, 29］. However, these studies assessed the peritumoral region on slides, and 3D investigation of tumor spread in the whole resected liver was not attempted. To our knowledge, this is the first report about the relation between feeding portal branches and the location of *vp/im* based on 3D images. For surgeons, it is extremely important to be able to predict how malignant cells spread to the surrounding liver parenchyma from the main HCC.

In the present series, *vp/im* were scattered extensively in the resected liver specimens of some patients. In particular, 3D mapping images suggested that *vp/im* could spread through the portal territories. Although we studied a limited number of patients, the distribution of *vp/im* tended to be more extensive in patients with larger HCCs than in those with smaller HCCs. In the patients with smaller HCCs, almost all *vp/im* were localized to the peritumoral region within 1 cm of the tumor margin, including micro tumor thrombosis. Furthermore, the patients with tumors 30-50 mm revealed high frequent *vp/im* compared with tumors less than 30 mm in this study. These findings suggested that tumor size is one of the clinical factors associated with metastasis［4-

6］.

Although it remains controversial as to whether the prognosis is better with anatomical resection than non-anatomical resection ［1-3］, anatomical resection of a solitary HCC 2 to 5 cm in size was recommended to reduce postoperative recurrence according to the large-scale study of the Liver Cancer Study Group of Japan［2］. However, it was also reported that there was no significant difference of postoperative recurrence between anatomical and non-anatomical resection for HCCs less than 2 cm in size. Non-anatomical resection has recently been accepted for carefully selected tumors, and our results support this strategy for relatively small tumors in terms of microscopic tumor cell clearance.

In case 5, several *vp/im* sites were a little apart from the main tumor and micro tumor thrombosis was seen at the proximal side in spite of the tumor being a smaller HCC. This case suggested that some tumors have a high malignant potential even while small in size. Macroscopically, this tumor was of the confluent multinodular type. The macroscopic type is generally considered to be one of the risk factors for portal vein invasion［30-32］. Therefore, we should be aware of the tumor type before deciding

on the extent of resection in order to achieve curability, even if a lesion is small.

One of the limitations of this study is single center and small sample size. To evaluate the optimal extent of resection, further study with more sample size including postoperative prognosis will be required. Also, we could only evaluate tumor spread in the resected portal territory, although there is a possibility of *vp/im* dissemination in another remaining portal territory surrounding the main tumor. In order to investigate the tumor spread of HCC precisely, a whole liver examination using transplantation explants is needed.

Conclusion

This study showed that 3D mapping images are helpful for assessing the pattern of tumor spread in patients with primary solitary HCC. Our results may have implications for understanding the mechanism of liver tumor spreading and the treatment strategy for HCC. Further analysis of more patients will be required to make definitive conclusions for the optimum extent of HCC resection with regard to portal spread.

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Figure legends

FIGURE 1. Flow chart of patients included in this study. †; lobectomy, central bisegmentectomy, segmentectomy, PVE; portal vein embolization, *vp/im*; microscopic portal vein invasion and/or intrahepatic metastasis

FIGURE 2. Diagram shows the steps for designing 3D-mapping images.

FIGURE 3. Total number and distance of *vp/im* lesions. Histogram shows the total number of *vp/im* lesions at each distance. "*vp/im*" were more frequent in larger HCCs than in smaller HCCs (195 vs. 126). In patients with smaller HCCs, one of 126 lesions (0.7%) was located over 1 cm from the tumor margin *versus* 20 of 195 lesions (10.2%) in patients with larger HCCs. Furthermore, four of 195 lesions (2.0%) were located over 2 cm from the main tumor in patients with larger HCCs.

FIGURE 4. Representative 3D mapping images of smaller HCCs (A, B: case 2, C-E: case 5). Dotted line shows the extent of resection in each case. The irregular semitransparent green region in each image shows the main tumor, while small red balls

indicate the sites of *vp/im*. Almost all the *vp/im* lesions were located within 1 cm of the tumor margin in all patients with smaller HCCs (B, D). Only 1 smaller HCC was associated with consecutive micro-tumor thrombosis from the main tumor in the proximal area toward the hilum (E; black arrow).

FIGURE 5. Representative 3D mapping images of larger HCCs (A, B: case 10, C, D: case 11). The majority of *vp/im* were scattered extensively as far as the 3rd order branches of the portal vein (B, D; arrow). The most distant *vp/im* were located 4 cm from the tumor margin (D; circle). P; portal vein, Vent; ventral vessel, Vent-inf; ventral inferior vessel

Tables

TABLE 1. Clinicopathological data of the 14 patients

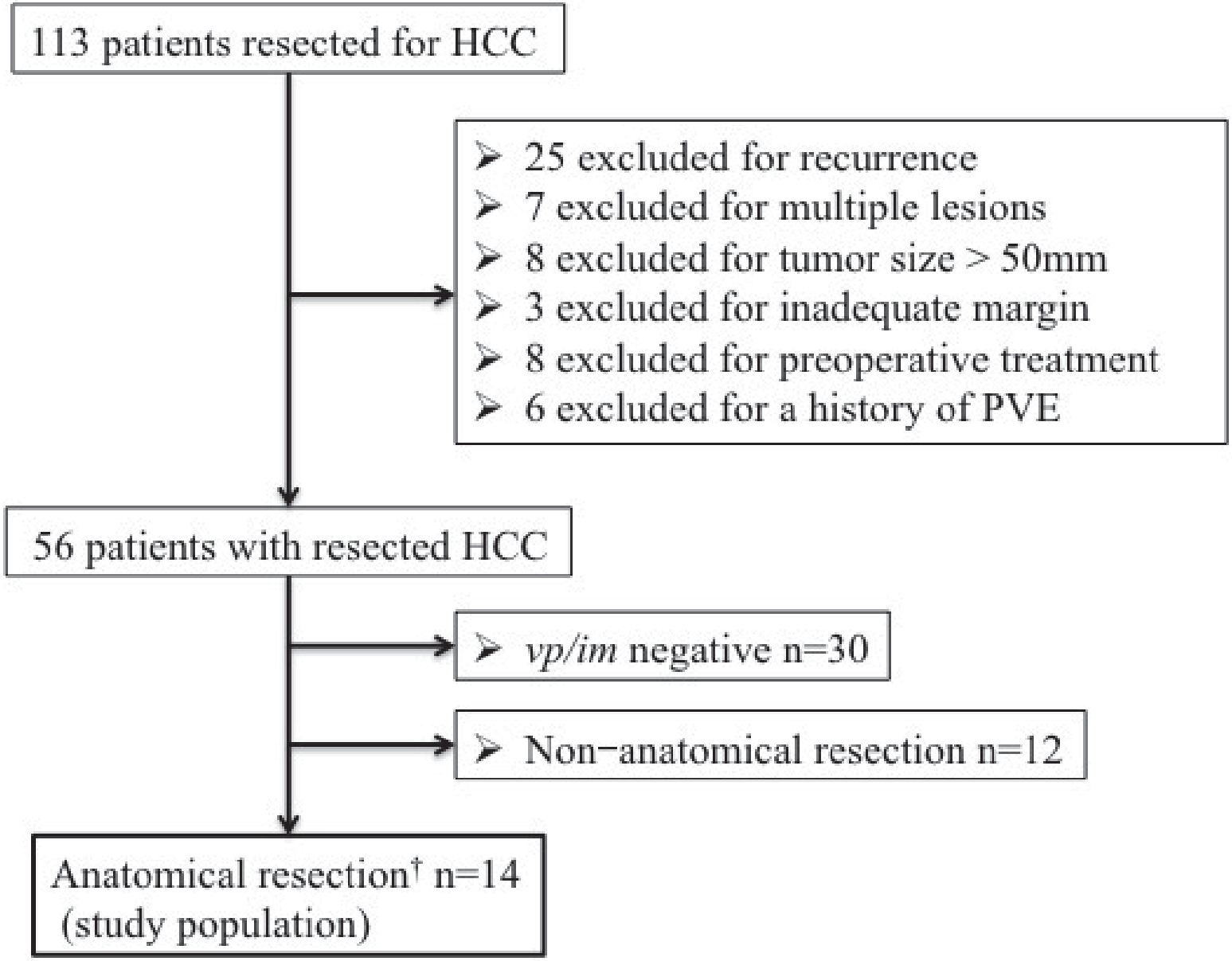
Age	68.5 (57-81)
Male/Female	9/5
B/C/both negative	0/10/4
Total bilirubin (mg/dl)	0.82 (0.28-1.53)
Albumin (g/dl)	4.125 (3.32-4.56)
Platelet count (10^3/μl)	17.0 (10.5-29.7)
PT (%)	93.5 (59-132)
ICG R_{15} (%)	15 (5-27)
HA (ng/ml)	47 (19-207)
AFP (ng/ml)	38.9 (1.8-7564)
AFP L3 (%)	33.3 (1.9-75.2)
PIVKA-Ⅱ (mAU/ml)	163 (24-3611)
Tumor size (mm)	26 (15-50)
Extent of hepatic resection segmentectomy/bisegmentectomy/lobectomy	9/3/2
Macroscopic classification SN/SNEG/CMN/INF	4/6/3/1
mod/mod-poor/poor/SC	10/1/2/1

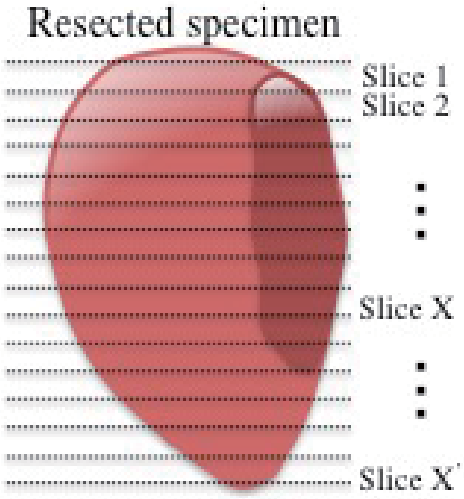
Categorical data are expressed as the number and continuous variables are expressed as the median (range). B; hepatitis B virus antigen positive, C; hepatitis C virus antibody positive, PT; prothrombin time, ICG R_{15}; indocyanine green retention rate at 15 minutes, HA; hyaluronic acid, AFP; α-fetoprotein, PIVKA; protein induced by vitamin K absence, SN; simple nodular type, SNEG; simple nodular type with extranodular growth, CMN; confluent multinodular type, INF; infiltrative type, mod; moderately differentiated hepatocellular carcinoma, mod-poor; moderately to poorly differentiated hepatocellular carcinoma, poor; poorly differentiated hepatocellular carcinoma, SC; hepatocellular carcinoma with sarcomatous change

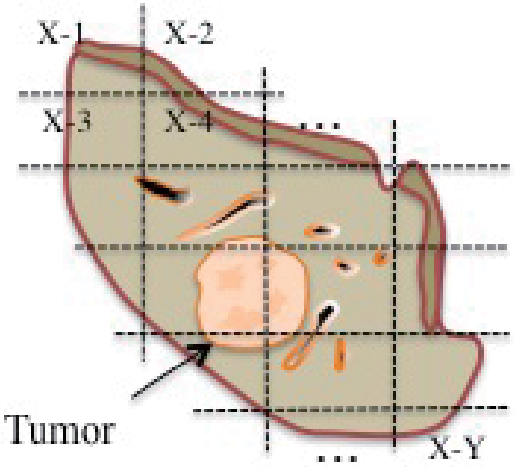
TABLE 2. Histological findings in the 14 patients

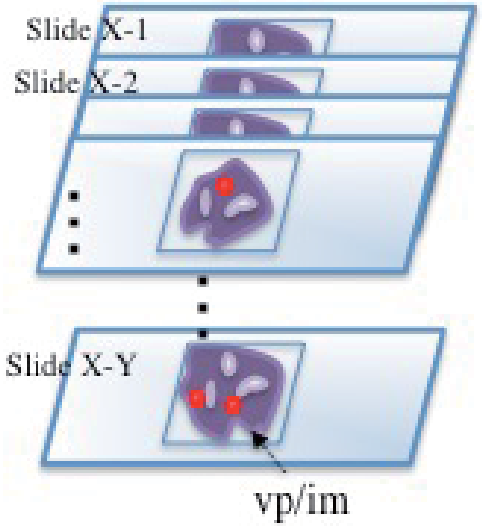
Case no.	Tumor size (mm)	Macro type	Histological grade	Extent of resection	Number of cut sections	Distance of *vp/im** (mm)
1	15	SNEG	mod	Seg	78	< 5
2	17	CMN	mod	Seg	191	< 5
3	18	SNEG	mod	Seg	169	< 5
4	20	SN	poor	Seg	78	< 5
5	20	CMN	mod	Bi	114	11
6	22	CMN	mod	Seg	39	< 5
7	22	SN	mod	Bi	155	< 5
8	30	SNEG	poor	Seg	154	< 5
9	30	SN	mod	Seg	57	< 5
10	40	SN	mod	Lob	73	22
11	40	INF	SC	Bi	109	40
12	40	SNEG	mod	Seg	70	17
13	42	SNEG	mod	Seg	76	5
14	50	SNEG	mod-poor	Lob	165	9

*Distance of the farthest *vp/im* lesion from the tumor margin, SN; simple nodular type, SNEG; simple nodular type with extranodular growth, CMN; confluent multinodular type, INF; infiltrative type, mod; moderately differentiated hepatocellular carcinoma, mod-poor; moderately to poorly hepatocellular carcinoma, poor; poorly differentiated hepatocellular carcinoma, SC; hepatocellular carcinoma with sarcomatous change, Seg; segmentectomy, Bi; central bisegmentectomy, Lob; lobectomy


113 patients resected for HCC
25 excluded for recurrence
7 excluded for multiple lesions
8 excluded for tumor size > 50mm
3 excluded for inadequate margin
8 excluded for preoperative treatment
6 excluded for a history of PVE
56 patients with resected HCC
vp/im negative n=30
Non−anatomical resection n=12
Anatomical resection† n=14
(study population)





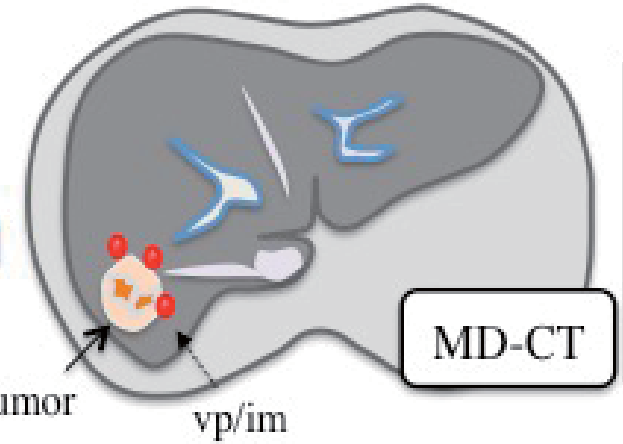


1. After fixed in 10% formalin, resected specimen was cut 5 mm thick slices in the axial plane.
2. Each slice was given a slice number.

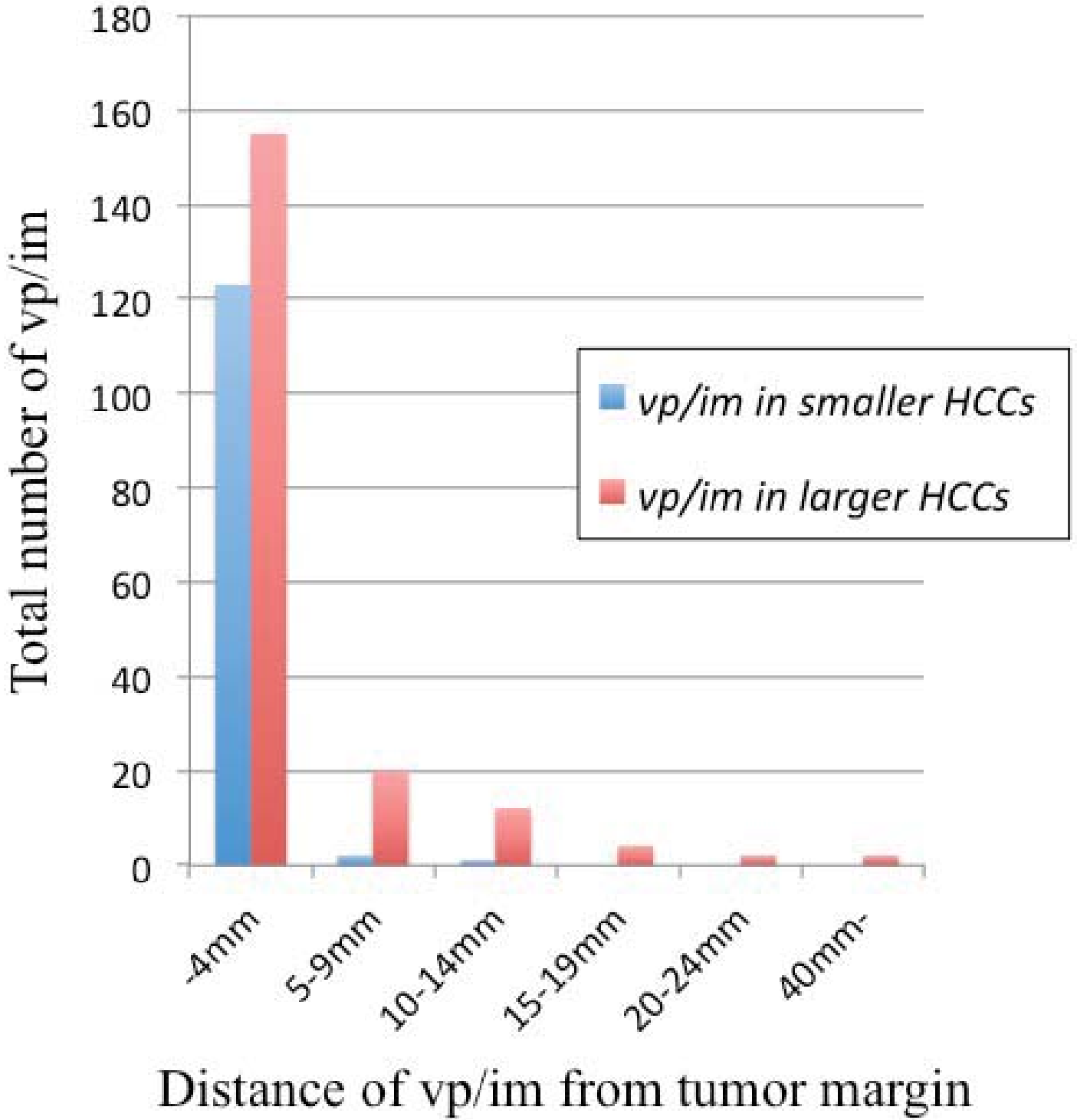
3. Each slice was divided into several tissue blocks sized for Path Cassettes®.
4. Each block of a slice was given a "slice-block" number.

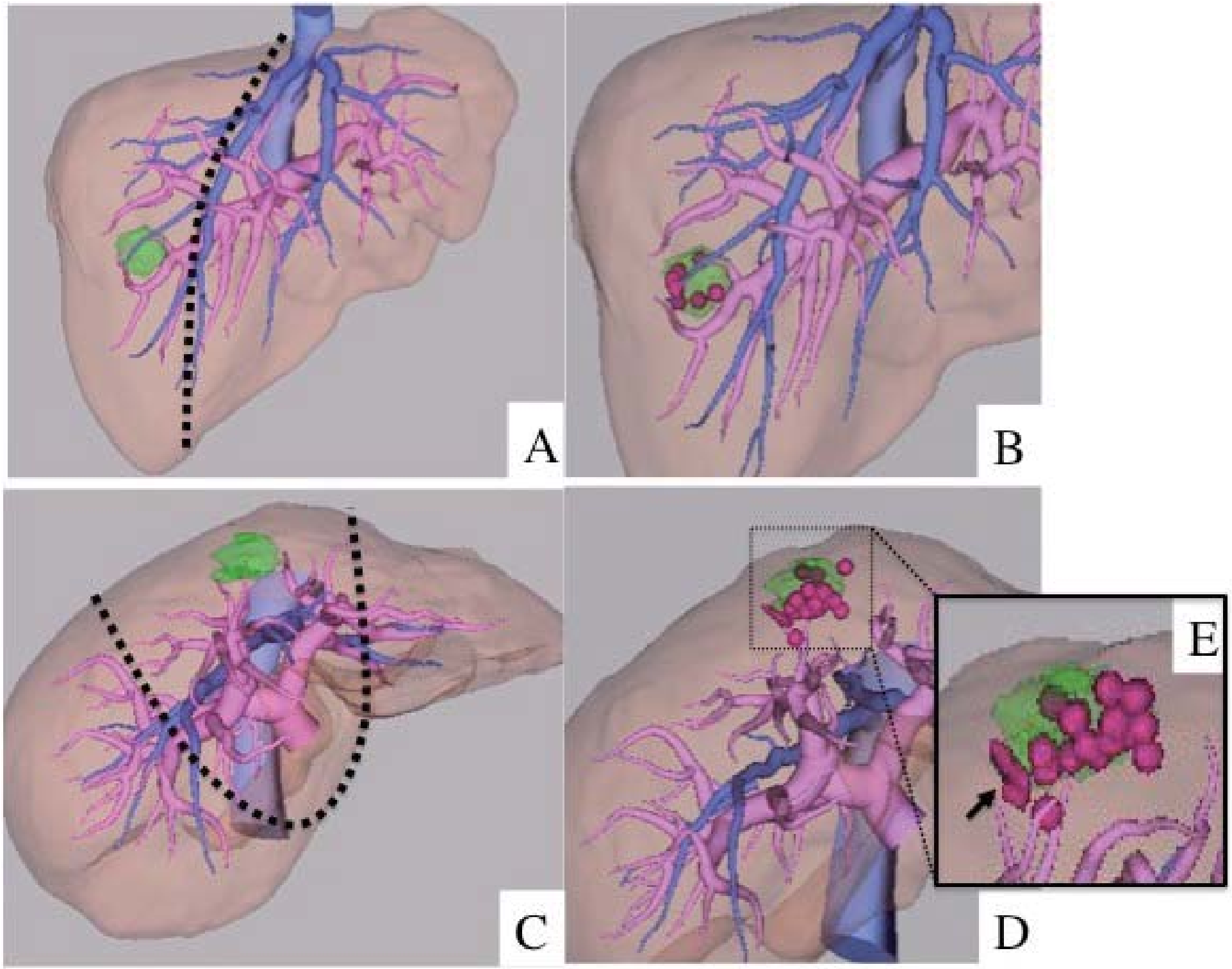
5. Histopathologic examination of each block was performed.
6. Each site of vp/im was detected on all slides and marked on the slide glass.

7. All the sites of vp/im were reproduced on the preoperative multi-detector CT images corresponding to the intrahepatic vessels.



3D reconstruction by SYNAPSE VINCENT®


180
160
140
120
100
80
60
40
20
0
Total number of vp/im
vp/im in smaller HCCs
vp/im in larger HCCs
-4mm
5-9mm
10-14mm
15-19mm
20-24mm
40mm-
Distance of vp/im from tumor margin


A
B
C
D
E