

RESEARCH ARTICLE

Evaluation of Computer-Assisted Quantitative Volumetric Analysis for Pre-Operative Resectability Assessment of Huge Hepatocellular Carcinoma

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Abstract

Purpose: Hepatic resection is arguably the preferred treatment for huge hepatocellular carcinoma (H-HCC). Estimating the remnant liver volume is therefore essential. This study aimed to evaluate the feasibility of using computer-assisted volumetric analysis for this purpose. **Methods:** The study involved 40 patients with H-HCC. Laboratory examinations were conducted, and a contrast CT-scan revealed that 30 cases out of the participating 40 had single-lesion tumors. The remaining 10 had less than three satellite tumors. With the consensus of the team, two physicians conducted computer-assisted 3D segmentation of the liver, tumor, and vessels in each case. Volume was automatically computed from each segmented/labeled anatomical field. To estimate the resection volume, virtual lobectomy was applied to the main tumor. A margin greater than 1 cm was applied to the satellite tumors. Resectability was predicted by computing a ratio of functional liver resection (R) as $(V_{\text{resected}} - V_{\text{tumor}}) / (V_{\text{total}} - V_{\text{tumor}}) \times 100\%$, applying a threshold of 50% and 60% for cirrhotic and non-cirrhotic cases, respectively. This estimation was then compared with surgical findings. **Results:** Out of the 22 patients who had undergone hepatectomies, only one had an R that exceeded the threshold. Among the remaining 18 patients with non-resectable H-HCC, 12 had Rs that exceeded the specified ratio and the remaining 6 had Rs that were < 50%. Four of the patients who had Rs less than 50% underwent incomplete surgery due to operative findings of more extensive satellite tumors, vascular invasion, or metastasis. The other two cases did not undergo surgery because of the high risk involved in removing the tumor. Overall, the ratio of functional liver resection for estimating resectability correlated well with the other surgical findings. **Conclusion:** Efficient pre-operative resectability assessment of H-HCC using computer-assisted volumetric analysis is feasible.

Keywords: Hepatocellular carcinoma - hepatectomy - function - volumetry

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Introduction

Liver cancer with a maximum diameter of 10 cm or greater is called huge hepatocellular carcinoma (H-HCC). The incidences of macrovascular invasion and multiple tumors are high in H-HCC. With the advancement in surgical techniques, equipment, and post-operative care, liver resection for patients with H-HCC can now be performed with low morbidity and mortality. Majority of current scholars believe that surgery is still preferred for H-HCC because it is the most effective treatment measure (Lee et al., 2007; Taniai et al., 2008). Hemihepatectomy or extended hemihepatectomy is generally performed. Pre-operative resectability assessment is particularly important to guarantee the safety and effectivity of the operation. Consequently, the evaluation of hepatic reserve is mandatory for hepatectomy candidates. Pre-operative measurements of normal liver resection volume and remnant liver volume are significant, in addition

to evaluation of the systemic and liver functions of the patients. In cases of H-HCC, surgery is necessary to minimize loss of normal liver tissue and avoid post-operative liver failure (Lee and Chen, 2005; Lodge, 2005; Karlo et al., 2010).

The hepatic function is complex, and a single, reliable liver function test is not yet available. Traditional methods for estimation of hepatic functional reserve, such as biochemical examinations of liver function and Child-Pugh classification, have been found to be limited in clinical practice (Tu et al., 2007). Thus, exploring more rational strategies for estimating hepatic functional reserve in pre-operative patients with H-HCC is important. Many studies have demonstrated that hepatic functional reserve is significantly correlated with liver volume. At least 16 different formulas for estimating the standard liver volume (SLV) have been published worldwide (Pomposelli et al., 2012; Tong et al., 2012). Given the extensive variability, care must be taken when a formula is being

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chosen for estimating SLV. CT-based liver volumetry has become one of the methods used to estimate the hepatic functional reserve of a patient. However, the operation of many measurement software thus far is complex, time-consuming, and subjective, and their clinical value on guidance is limited. With the continuous development of computer technology, several intelligent, software-assisted image post-processing programs have been developed to provide a more accurate volume measurement, with quicker and more convenient application.

Our study aims to evaluate the clinical value of computer-assisted quantitative volumetric analysis for pre-operative resectability assessment of H-HCC to help patients determine the most appropriate treatment plan.

Materials and Methods

Patients

From September 2009 to July 2010, 40 patients with H-HCC who had undergone multidetector computed tomography (MDCT) were examined. All patients (10 without underlying liver disease and 30 with chronic hepatitis or light/moderate cirrhosis) were grade A according to the Child–Pugh classification and had acceptable liver functions. Patients who have extrahepatic metastases were excluded. Pre-operative dual-phase contrast CT-scan revealed 30 cases with single lesion and 10 cases with multiple ones (each with less than three satellite tumors with diameter of 3 cm or smaller in the other liver segments). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Zhongshan Hospital Fudan University. Written informed consent was obtained from all participants.

CT Protocol

CT was performed with a 16-section scanner (Siemens Sensation) or a 64-section scanner (GE Lightspeed). A multisection CT protocol was used to acquire a set of liver dual-phase images for pre-operative CT (arterial and portal venous phases) evaluation of liver morphology and vascular anatomy. The scans for dual phase were acquired at fixed delays (30 s [arterial phase] and 70 s [portal venous phase]) after the administration of 2 mL per kilogram of body weight of non-ionic contrast material at a rate of 3 mL/s using a pump through a peripheral vein. A section thickness of 5 mm (without overlaps) which was automatically generated by the workstation after scanning was used for volumetry.

Volumetric Measurement and Hepatectomy Simulation

All CT images were sent to an IQQA-Liver Workstation. Real-time interactive computer tools (IQQA-Liver, EDDA Technology) were used by two radiologists to conduct computer-assisted 3D segmentations of liver, tumor, and artery/portal vein/hepatic vein by consensus. CT volumetry, 3D reconstruction of hepatic veins and portal vein, and hepatectomy simulation were performed on the scans obtained during the portal venous phase. Reconstruction of hepatic artery and volumetric measurement of some satellite tumors shown only on the

hepatic arterial phase were performed on images obtained during the arterial phase.

The volumetric measurements were performed on MDCT images of the liver, with semiautomatic tracing of liver boundaries and tumor contours in multiple sections by means of dedicated software programs. The results were not manually outlined on each axial image, but they were outlined whenever the contour of the liver or the tumor considerably changed. The contours of intermediate slices were automatically interpolated and, if needed, manually corrected by the reader. The 3D images of liver parenchyma and tumor were reconstructed by software. Ultimately, the volumes of the liver and the tumor were automatically calculated. Large vessels, including the inferior vena cava and the extrahepatic portal vein, the major fissures, and the gallbladder fossa were excluded. In addition, 3D reconstructions of the portal vein, hepatic vein, and hepatic artery were performed. Then, the 3D images of the liver parenchyma, tumor, portal vein, hepatic vein, and hepatic artery were overlapped to create integrated 3D images that showed tumor localization and provided detailed hepatic vascular anatomy and macrovascular invasion.

Pre-operative hepatectomy simulation was performed using real-time interactive computer tools (IQQA-Liver). Hemihepatectomies, extended hemihepatectomies, and other hepatectomies that were more than two segments were applied for the removal of the main large tumors. The hepatic veins, portal vein, falciform ligament, gallbladder fossa, and inferior vena cava were used to determine the respective borderlines of the segments. In case of satellite tumors, a margin greater than 1 cm was applied. Then, the ratio of liver resection (R1), the ratio of functional liver resection (R2), and the ratio of future liver remnant (RFLR) were calculated using the following formula (Kubota et al., 1997; Gazzaniga et al., 2005):

$$R1 = (V_R / V_W) \times 100\%; R1FLR = 1 - R1$$

$$R2 = ((V_R - V_T) / (V_W - V_T)) \times 100\%; R2FLR = 1 - R2$$

The abbreviations used are the following: V_R = resected liver volume including the tumor; V_W = whole liver volume including the tumor; V_T = tumor volume; R1 is the ratio of V_R to V_W and R2 is the ratio of the nontumorous parenchymal volume of the resected liver to that of the whole liver; R1FLR is the ratio of future liver remnant volume to the whole liver volume and R2FLR is the ratio of future liver remnant volume to the nontumorous parenchymal volume of the whole liver.

Statistical Analysis

RFLR thresholds of 50% and 40% for patients with chronic liver diseases and without underlying liver disease, respectively, were applied to predict the resectability of H-HCC. When RFLR exceeded the threshold, the resection was believed to be safe. This estimation was then compared with surgical findings.

Results

Surgical Procedures and Findings

Up to 22 patients with H-HCC, including four with tumor diameter ≥ 15 cm, underwent different types of

Table 1. Liver Diseases, CT Volumetric Data, and Procedures of Hepatectomy of Resectable Cases (n=22)

Patient no.	Liver diseases	Maximum diameter of tumor (cm)	Number of satellite tumors (cm)	R ₁ (%)	R ₂ (%)	Resected liver lobe/segments
1	without	12	0	68.8	52.2	right hepatic lobe
2	without	16	0	71	33.8	right hepatic lobe
3	without	16	0	80.6	47.2	right hepatic lobe+partial IV
4	without	13	2 (0.5, 2.0)	79	59	right hepatic lobe+partial IVa+III
5	without	10	0	36.5	15.5	VI, VII
6	without	11	0	39.4	20.2	I, II, III
7	light liver cirrhosis	11.7	multiple ones in same lobe	53.2	49.1	right hepatic lobe
8	light cirrhosis	14	0	72.4	45.5	right hepatic lobe
9	moderate cirrhosis	10	0	48.4	29	right hepatic lobe
10	moderate cirrhosis	11	1 (1.0)	44.8	21	left hepatic lobe +partial V
11	light cirrhosis	11	1 (1.5)	42.1	24.6	left hepatic lobe +partial V
12	chronic hepatitis	14	1 (2.0)	34	14.6	left hepatic lobe +partial VII
13	light cirrhosis	13	0	45	17	left hepatic lobe
14	light cirrhosis	18	1 (1.0)	67.2	50.6	V, VI, VII+partial III
15	moderate cirrhosis	16	1 (0.8)	52.8	22.2	V, VI, VII+partial VIII
16	light cirrhosis	14	0	43.7	17.3	VI, VII
17	moderate cirrhosis	13.8	0	47.4	23.4	II, III
18	moderate cirrhosis	14.8	0	34.8	4.5	II, III
19	light cirrhosis	10	0	42.9	21.5	V, VI
20	moderate cirrhosis	10	0	46.2	25.7	II, III
21	moderate cirrhosis	10	0	46.4	29.7	V, VIII
22	moderate cirrhosis	13.7	0	51.7	16.6	VI, VII +the right hepatic vein

Table 2. Liver Diseases, CT Volumetric Data, and Surgical Findings or Pre-operative Clinic Estimations of Nonresectable Cases (n=18)

Patient no.	Liver diseases	Maximum diameter (cm)	satellite tumor	R ₁ (%)	R ₂ (%)	surgical findings or pre-operative clinical estimations
1	without	18	no	91.1	72	According to the pre-operative clinical estimations, patients of no. 1 to 12 with massive HCC and low potential hepatic functional reserve were not appropriate for hepatic resection. TAE (transarterial embolization) or the other nonsurgical treatment options were performed.
2	without	12	no	87.2	74.6	
3	without	14	no	76.3	61.2	
4	without	17.9	yes	82.3	63.2	
5	liver cirrhosis	14	no	67	60.7	
6	light cirrhosis	12	yes	66	56.9	
7	moderate cirrhosis	15	no	78	53.4	
8	moderate cirrhosis	18.8	yes	84.7	52.6	
9	moderate cirrhosis	24	no	84.8	53.3	
10	liver cirrhosis	18	no	73.9	55.1	
11	chronic hepatitis	13.5	no	72.6	51.4	
12	moderate cirrhosis	21	no	84.8	59.1	
13	liver cirrhosis	22.5	no	75.3	41.5	
14	chronic hepatitis	16.5	no	78.9	48	
15	moderate cirrhosis	13.5	no	43.4	24.2	
16	light cirrhosis	15	no	69.8	47.9	
17	liver cirrhosis	10.9	no	46.2	30.5	
18	moderate cirrhosis	12	no	36.1	15.3	

hepatectomies. Right or extended right hepatic lobectomy (RHL or ERHL), left or extended left hepatic lobectomy (LHL or ELHL), and other types of hepatectomy with more than two segments were performed in 7, 4, and 11 patients, respectively. Among 18 patients with nonresectable H-HCC (including 10 with tumor diameter ≥ 15 cm), 14 cases did not undergo surgery because of the low potential hepatic functional reserve and 4 cases had incomplete surgery due to operative findings of more extensive satellite tumors, vascular invasion, or metastasis.

Volumetric Data

The history of liver disease, CT findings, and volumetric data, including tumor sizes, satellite tumors,

R1s, R2s and procedures of hepatectomy, of 22 patients who underwent liver resection are summarized in Table 1 and Figure 1. The differences between R1s and R2s were remarkable. Although the R1s of 5 with chronic liver disease and 4 without underlying liver disease of 22 patients exceeded 50% and 60%, respectively (the highest was 80.6%), the R2s of only 1 with chronic liver disease of all patients slightly exceeded this level. Using R1FLR to predict resectability before surgery, 9 of 22 patients who underwent liver resection were found to be nonresectable. Only one case was not in agreement with the surgical findings obtained using R2FLR for prediction.

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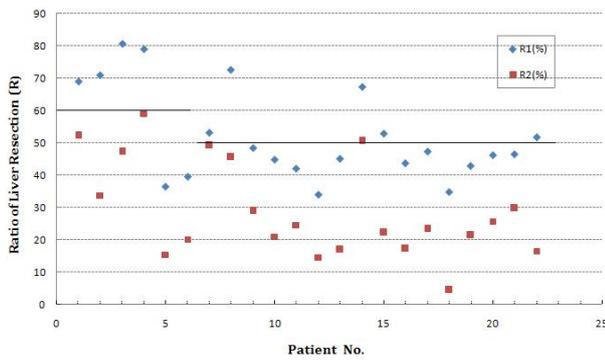


Figure 1. The Scatter Diagram of R1 and R2 of Resectable Cases (n=22)

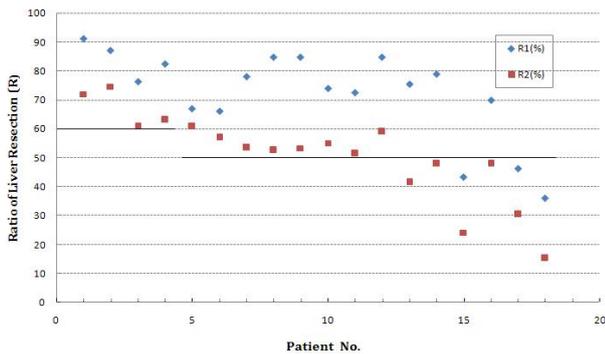


Figure 2. The Scatter Diagram of R1 and R2 of Nonresectable Cases (n=18)

R1s, R2s and surgical findings or pre-operative clinical estimations, of 18 patients with nonresectable H-HCC are summarized in Table 2 and Figure 2. The R1s of all patients exceeded 60% (the highest was 91.1%, with a mean of 79.1%±8.0%). The R2s of 4 without underlying liver disease and 8 with chronic hepatitis or liver cirrhosis exceeded 60% and 50%, respectively (mean: 59.5%±7.5%). The R2s of the other 6 cases with liver diseases were < 50%. Four of six cases with R2s < 50% had incomplete surgery due to operative findings of more extensive satellite tumors, vascular invasion, or metastasis. Two cases whose R2s were 41.5% and 48% did not undergo surgery because of the high risk in massive tumor removal.

Discussion

Although various treatments for H-HCC have been applied in clinical practice, hepatic resection remains the most effective because it offers the possibility of long-term survival (Lee et al., 2007; Taniai et al., 2008). However, resection of H-HCC is associated with an increased risk of operative morbidity and mortality largely due to liver failure, compared with small HCC. The risk of post-operative liver failure depends on the quantity and the quality of the liver parenchyma spared by resection. Therefore, evaluation of hepatic reserve is mandatory for hepatectomy candidates.

The liver has one of the most complex functions among the different organs in the human body. Thus, a single, reliable liver function test is not yet available. The simplest and most common assessment relies on the Child–Pugh classification, which includes clinical (ascite

and encephalopathy) and laboratory (serum bilirubin, albumin, and prothrombin time) parameters. Generally, Child A patients can tolerate removal of up to 50% of liver parenchyma, whereas only limited resection is allowed in Child B patients. Resection is contraindicated in Child C patients (Gazzaniga et al., 2005). The risk of Child A patients for operation depends on the liver parenchyma spared by the resection. Most patients with HCC in China have chronic hepatitis or liver cirrhosis, and an inadequate amount of functional residual liver tissue after resection potentially leads to acute liver failure (Schindl et al., 2005; Suman and Carey, 2006). Therefore, pre-operative estimation of liver volume is important to assess hepatic functional reserve.

Different techniques can be used to estimate liver volume in vivo (Kayaalp et al., 2002; Luccichenti et al., 2003; Emirzeoglu et al., 2005; Muller et al., 2010; Torkzad et al., 2012; Aoyama et al., 2013). Advancements in radiological techniques have enabled the acquisition of MDCT images with fairly high temporal and spatial resolutions, which may be applied in accurate pre-operative assessment of the resected liver volume and future liver remnant volume by CT volumetry. A particular advantage of CT volumetry is that the tumor and nontumorous parenchymal volumes can be separately measured. Accurate 3D visualization images of the liver based on MDCT images can show the spatial relations between vessels and tumors from different directions as needed, and can be used for pre-operative measurement of liver volume, hepatectomy simulation, and estimation of residual liver volume (RLV) (Numminen et al., 2005; Satio et al., 2005).

Given the wide variability of patients’ liver volumes, only RLV cannot predict the post-operative liver function. At present, estimation of the standard liver volume (SLV) is the more widely applied method in clinical practice (Pomposelli et al., 2012; Tong et al., 2012). SLV and body surface area (BSA) can be calculated by a formula according to the height and weight of the patient. Standardized future liver volume (SFLV) is then computed as RLV/BSA, and SFLV ratio is computed as RLV/SLV. Generally, hepatectomy can be safely performed in patients with normal liver function when they have SFLV of over 250 ml or SFLV ratio over 25% to 30%. However, the SFLV ratio of patients with hepatic dysfunction or cirrhosis must exceed 40% (Shirabe et al., 1999; Shoup et al., 2003; Schroeder et al., 2006; Clavien et al., 2007; Suda et al., 2009).

Hepatic functional reserve is highly related to the quantity and quality of liver cells. Several researchers have reported that the larger the resected normal liver volume, the greater the risk of liver failure (Tu et al., 2007). Therefore, after excluding the tumor volume, estimating the percentage of the resected nontumorous parenchymal volume (R2) is necessary (Kubota et al., 1997; Gazzaniga et al., 2005) because it reflects the functional parenchymal or effective resection ratio and indicates the amount of normally functional liver that was lost. Thus, R2FLR can accurately predict the post-operative function of the liver remnant. Kubota et al. (1997) suggested that patients with normal liver function and those with indocyanine

green retention rate after 15 min (ICG15) values < 20% can tolerate resection of up to 60% and 50% of the nontumorous parenchyma.

In our study, all the patients had H-HCC with maximum diameters of 10 cm or greater, including 14 with tumor diameter ≥ 15 cm. The removal of huge tumor is technically difficult and entails high risks. Among 22 patients who underwent liver resection, the R1s of 5 with chronic liver disease and 4 without underlying liver disease exceeded 50% and 60%, respectively (the highest was 80.6%), whereas the R2s of only 1 with chronic liver disease slightly exceeded this level. The results indicate that the amount of normal functioning liver lost due to hepatectomy in these patients was limited, but the resected volume, including the tumor, was large. Therefore, the patients tolerated the operations well. Among 18 patients with nonresectable HCC, the R2s of six cases were < 50%. Four of them had incomplete surgery due to operative findings of more extensive satellite tumors, vascular invasion, or metastasis. Only two cases with tumor diameter ≥ 15 cm and whose R2s approached 50% did not undergo surgery because of the high risk in the massive tumor removal.

Our results suggest that H-HCC patients without underlying liver disease and with chronic hepatitis or cirrhosis and who are under the category of Child a can undergo resection of up to 60% and 50% of the functional liver parenchyma, respectively. Therefore, resection is safe when the ratio of future functional liver remnant (R2FLR) exceeds the threshold of 40% and 50%. To evaluate resectability using the ratio of future liver remnant including tumor (R1FLR), the number of potential surgical candidates may be reduced. Nevertheless, as surgical procedures that involve resection of massive HCC with maximum diameter ≥ 15 cm are occasionally associated with high risks, such as post-operative liver failure, the decision to perform such should be made with care for each individual even if the R2FLR exceeds the threshold.

Compared with the methods of evaluation of SFLV, pre-operative resectability assessment using R2 and R2FLR without measurement of weight and height of the patients in our study is more convenient and intuitive, and applies to hemihepatectomy as well as other types of hepatectomy of more than two segments.

Resection of H-HCC remains one of the most difficult operative procedures because of anatomical complexity and hepatic vascular variability. Moreover, H-HCCs often press or invade crucial structures, such as major vessels and bile ducts, or are accompanied with cancerous emboli in portal veins or bile ducts. Injury of the vascular and bile duct, which is directly associated with massive bleeding and high morbidity and mortality, can occur during dissection. In our study, 3D visualization images of liver based on virtual technique improved the surgeon's knowledge of liver anatomy and made planning of operations possible. However, without knowledge of major blood vessels or other important structures related to the tumor, hepatectomy cannot be curatively and safely performed. Accurate 3D images of the liver showing the spatial relations between vessels and tumors from different directions as needed on a screen may further

help the surgeon in perceiving the optimal resection line. Significant vessels crossing the resection line are readily visible and bleeding is minimized without unnecessary damage to other vessels. Therefore, 3D visualization images for pre-operative hepatectomy simulation can make complicated liver resection safe and successful.

In conclusion, efficient pre-operative resectability assessment of H-HCC using real-time computer volumetric segmentation, measurement, and virtual resection tools is feasible.

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