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Limited Excised Functional Liver Tissue in Hepatectomy for Large Hepatic Tumors Proved by a Three-Dimensional Reconstruction Technique

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Abstract: Three-dimensional (3D) reconstruction techniques have been widely used in the preoperative evaluation of hepatectomy. Here we used a 3D reconstruction technique to estimate the remnant liver volume and clarify a clinical speculation that limited functional liver tissue would be excised in hepatectomy for large hepatic tumors. Hepatectomy simulation by IQQA-Liver software was applied to 108 patients of hemihepatectomy divided into two groups (tumor diameter ≥ 10 cm vs.<10 cm). Liver volume (LV), standard liver volume (SLV), tumor volume (TV), functional liver volume (FLV), excised liver volume (ELV), excised functional liver volume (EFLV) and residual liver volume (RLV) were measured. Then we compared the rate of total liver resection (ELV/LV), the rate of functional liver resection (EFLV/FLV), and the relative rate of future liver remnant (RLV/FLV and RLV/SLV) between the two groups. The ELV calculated by the 3D reconstruction procedure were highly consistent with the actual liver excised volume ($r=0.994$, $p<0.001$), showing the accuracy of the simulation. Significantly smaller EFLV/FLV was seen in patients with a tumor diameter ≥ 10 cm than in patients with a tumor diameter<10 cm ($p<0.01$), in both the right and left hemihepatectomy subgroup. In contrast, significantly larger RLV/FLV was seen ($p<0.01$), and there was no difference of the RLV/SLV ($p>0.05$). Twenty-five patients had RLV/LV<30%, a recognized ratio of future liver remnant for safe hepatectomy. However, only one patient had RLV/SLV<30%. 97.2% of the patients had RLV/FLV>40%, and 98.1% had RLV/SLV>40%, accounting for the overwhelming majority of all patients. There was no hepatic failure or death within 30 days of surgery. In summary, it is better to use a 3D reconstruction method for preoperative safety assessment of liver resection for large hepatic tumors, through the hepatectomy simulation and volume calculation. In the same range of anatomical hepatectomy, a larger tumor mass meant less excised functional liver volume and more remnant liver volume. Our results indicated that neither ELV nor RLV/LV, but RLV/SLV was the better determinant of safety of hepatectomy.

Keywords: Three-Dimensional Reconstruction Technique, Hepatectomy Simulation, Huge Hepatic Tumor, Functional Liver Tissue, Residual Liver Volume

1. Introduction

Liver resection of hepatic tumors is the first line treatment option for curative intent, and in order to accomplish free surgical margins, an extended hepatectomy is required. Persistent improvements in hepatic surgical techniques and perioperative management have made partial hepatectomy safer, and increased the number of patients who could undergo extended hepatectomy with curative intent. At present, even for the huge (≥ 10cm) hepatic tumors, hepatic resection is regarded as a relatively safe and effective treatment for selected patients, provided that the patient's hepatic functional reserve is acceptable for resection [1-5].

However, extended liver resection for large hepatic tumors is associated with more complications and higher mortality after surgery. Usually, hemihepatectomy or extended hemihepatectomy is performed to achieve curative resection. The rates of postoperative hepatic failure increase as the degree of resection is extended [6-8]. Nevertheless, in clinical observation, we found that although resection of large hepatic tumors was generally accompanied by a larger excision liver volume (including the tumor), the amount of normal functional liver lost was limited as most of the resected liver was tumors. Therefore, a larger tumor-free residual volume would remain, and the patients might tolerate the operations with a lower likelihood of postoperative liver failure.

At present, preoperative measurements of excised liver volume and residual liver volume are important to evaluate the safety of major hepatectomy, in addition to assessing the patient's general condition and liver function [9-11]. With the advancement of computer technology, the computer tomography (CT)-based liver three-dimensional (3D) reconstruction technique not only permits detailed reconstruction of the spatial relations between vessels and tumors, but also offers an accurate preoperative virtual surgical planning and liver volume measurement [12-18].

In this study, we applied 3D reconstruction software to virtually simulate hemihepatectomy. We retrospectively analyzed the correlation between tumor size and the relative amount of excised liver volume and future liver remnants. The biochemical and clinical outcomes of patients who underwent the anticipated resections were correlated with tumor size and future liver remnants estimated preoperatively. We sought to clarify that limited functional liver tissue would be recected in anatomical hepatectomy for large hepatic tumors, and to assess the safety of resection.

2. Patients and Methods

2.1. Patients

From January 2018 to October 2021, 108 patients with liver solid tumor who underwent hemihepatectomy and underwent multidetector computed tomography (MDCT) as part of their preoperative assessment at the hepatic center of Tongji Hospital, Wuhan, China were examined retrospectively. Among them, 63 patients underwent right hepatectomy and 45 patients underwent left hepatectomy. All patients were divided into two groups: maximum tumor diameter ≥ 10cm (group A; 66 patients) and maximum tumor diameter<10cm (group B; 42 patients). Underlying tumors were hepatocellular carcinoma (n=85), cholangiocellular carcinoma (n=17), focal nodular hyperplasia (n=1), gastrointestinal stroma tumor (n=2), metastases of colorectal cancer (n=2), and solitary fibrous tumor (n=1). Preoperative clinical data are listed in Table 1. All patients provided written informed consent, and the study was approved by the local institutional review committee.

2.2. CT Protocol

All patients underwent preoperative MDCT using a 64-slice spiral CT scanner (GE Healthcare, USA) with a slice thickness of 1.25 mm. Both nonenhanced and three-phase contrast enhanced scans (arterial, portal venous, and delayed phases) were performed.

2.3. Three-Dimensional Reconstruction Analysis and Hepatectomy Simulation

All CT images were sent to 3D reconstruction software named IQQA-Liver (EDDA Technology, USA) for volumetric analysis and hepatectomy simulation. The 3D images of liver parenchyma and tumor were reconstructed by the software semiautomatically and manually reconciled when needed. Then the volumes of the liver and the tumor were automatically calculated. In addition, 3D reconstructions of the portal vein, hepatic vein, and hepatic artery were performed. Then, integrated 3D images that showed tumor localization and provided detailed hepatic vascular anatomy were created. The model of the whole liver was then subjected to virtual anatomical hepatic resection according to the operative strategy for each individual patient. We followed Couinaud's classification for the definition of anatomic divisions of the liver. The hepatic veins, portal vein, falciform ligament, gallbladder fossa, and inferior vena cava were used to determine the respective borderlines of the segments. Types of liver resection included either right hepatectomy or left hepatectomy. When the type of resection actually performed was different from that estimated preoperatively, the simulation was repeated. For example, a right hepatectomy would be simulated by virtual resection of the 3D liver model along a plane passing immediately to the right of the middle hepatic vein and extending directly to the inferior vena cava (Figure 1).

We measured the liver volume (LV), tumor volume (TV), functional liver volume (FLV=LV-TV), excised liver volume (ELV), excised functional liver volume (EFLV=ELV-TV), residual liver volume (RLV=LV-ELV), and standard liver volume [SLV (ml)=11.5 × body weight (kg) + 334)] [19]. Subsequently, the ratio of total liver resection was calculated as ELV/LV, the ratio of functional liver resection was calculated as EFLV/FLV, and the relative amount of future liver remnant was calculated as RLV/LV, RLV/FLV and RLV/SLV [20, 21].

2.4. Surgical Procedures

All patients underwent hemihepatectomy according to the preoperative hepatectomy simulation plan. Liver resection for hemihepatectomy was performed as previously described [22, 23]. Some of the patients had undergone laparoscopic hepatectomy. We first controlled the corresponding inflow and outflow vessels supplying the side of the liver to be resected. The inferior vena cava below the liver was clamped simultaneously in some patients to control bleeding [24]. No patient underwent total vascular exclusion. We then transected the liver parenchyma and the hepatic vein draining the part of the liver to be resected was ligated and divided intrahepatically. The resected liver surface was well processed to prevent bleeding and bile leakage without mattress suture.

2.5. Validation of Hepatic Volumetry

To validate the volumetric accuracy of the simulation system, the predicted liver resection volume was compared to the actual excision liver volume (AELV), which was measured by the water displacement method.

2.6. Postoperative Course

The operative time, intraoperative blood loss, postoperative complications, mortality, and hospital stay were recorded. Perioperative mortality was defined as any death within 30 days of surgery. To observe the postoperative recovery of liver function, liver function tests were sampled routinely on postoperative days (PODs) 1, 3, 5, 7 and 9. Glutamic-pyruvic transaminase (ALT), prothrombin time (PT) and total serum bilirubin (SB) were used to reflect liver cell injury conditions and liver synthetic and excretory functions respectively. Postoperative hepatic dysfunction was defined as bilirubin level>50 mmol/L or prothrombin time>18 s on postoperative day 5 or thereafter in this study [25].

2.7. Statistical Analysis

SPSS software version 19.0 (IBM, United States) was used for statistical analysis. All numeric data are presented as the means±standard deviation (SD) unless otherwise stated. Comparisons between groups were performed using the chi-square test or Fisher exact test for categorical variables and Student's t test for continuous variables. Correlations, shown with scatter plots, were analyzed using the Pearson's correlation test. $P<0.05$ was considered significant.

3. Results

3.1. Patients' Characteristics

Of the 108 patients enrolled in the study, all had complete simulation data and subsequently underwent hemihepatectomy. The patients' clinicopathological characteristics in relation to these two groups are shown in Table 1. The preoperative Child-Pugh classification, indocyanine green retention rate at 15 min (ICGR15), number of hepatitis B Virus (HBV) infections, presence of cirrhosis, operation time and intraoperative blood loss all showed no significant difference between the two groups. The ICGR15 ranged from 0.3% to 15.8% with a median of 4.3%. The mean postoperative hospital stay was 10.4±6.7 and 10.0±6.2 days, respectively (p=0.783). There were no major complications requiring additional surgery. Minor complications such as ascites, pleural effusion, wound infection, or bile leakage recovered well after conservative treatment.

Table 1. *Clinical characteristics of patients who underwent hemihepatectomy with either tumor size ≥10 cm or<10 cm (n=108).*

Clinical characteristics	Group A (≥10cm, n=66)	Group B (<10cm, n=42)	P value
Age (years)	48±12	51±12	0.179
Gender (M/F)	54:12	30:12	0.205
HBV, n (%)	52 (78.8%)	28 (66.7%)	0.161
ALT (U/L)	36.0±20.7	29.6±30.8	0.203
PLT (*10^9/L)	198±76	179±61	0.168
Child-Pugh class			1
A	65	41	
B	1	1	
Mean ICGR15 (%)	5.2±3.4	5.0±3.5	0.860
Tumor number			0.254
Single	47	34	
Multiple	19	8	
Tumor size (cm)	14.0±2.7	6.3±1.9	<0.001
Liver cirrhosis, n (%)	38 (52.4%)	22 (57.6%)	0.596
Hepatectomy			<0.001
Right	48	15	
Left	18	27	
Operation time (min)	255±81	247±75	0.709
Blood loss (ml)	489±120	401±131	0.156
Postoperative hospital stay (days)	10.4±6.7	10.0±6.2	0.783
Complications			
ascites	22	13	0.836
pleural effusion	38	27	0.487
wound infection	2	1	1
bile leak	2	1	1
hepatic dysfunction	9	2	0.246

All numeric data were presented as mean±standard deviation (SD) unless otherwise stated. HBV=Hepatitis B Virus; ALT=glutamic-pyruvic transaminase; PLT=blood platelet count; ICGR15=indocyanine green retention rate at 15 min. Tumor size: largest diameter of largest tumor in cm.

3.2. Validation of Simulation and Volumetric Data

3D reconstruction of the liver clearly illustrated the positional relationship among the liver, lesions, and hepatic blood vessels and simulation was performed according to anatomical hemihepatectomy (Figure 1). There was no significant difference between the estimated ELV of the simulation and AELV of the resected specimens (1034±592 and 1012±547 ml, p>0.05). The simulation showed high positive correlation (r=0.994, p<0.001; Figure 2A) between estimated ELV and AELV with a mean absolute error of 21.8 ml, and a high positive correlation (r=0.960, p<0.001; Figure 2B) between the maximum tumor diameter and estimated TV.

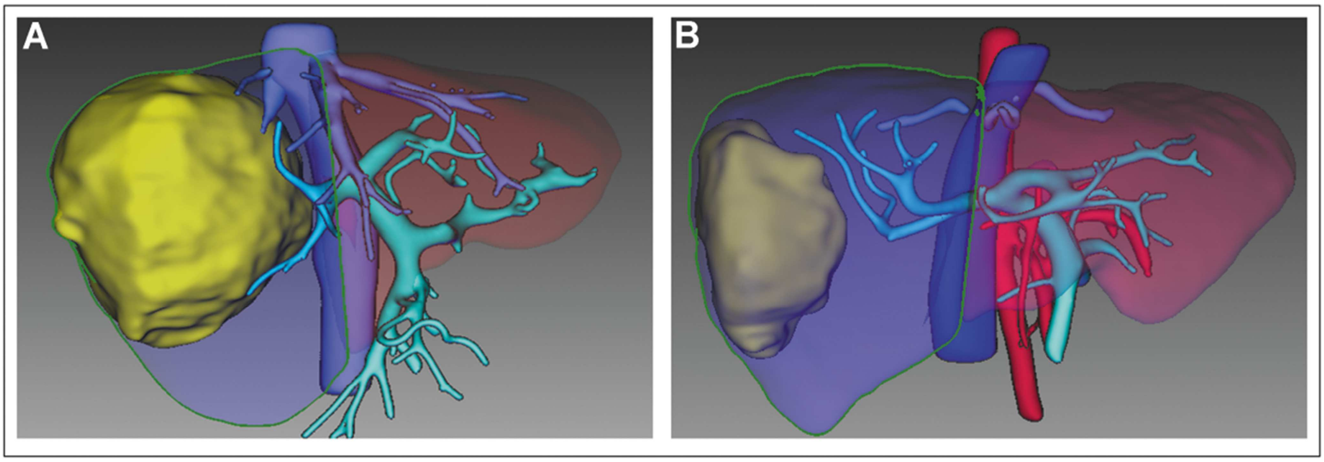

Figure 1. *Right hepatectomy simulated by virtual resection of the three-dimensional liver model along a plane passing immediately to the right of the middle hepatic vein and extending directly to the inferior vena cava. A. tumor size>10 cm; B. tumor size<10 cm.*

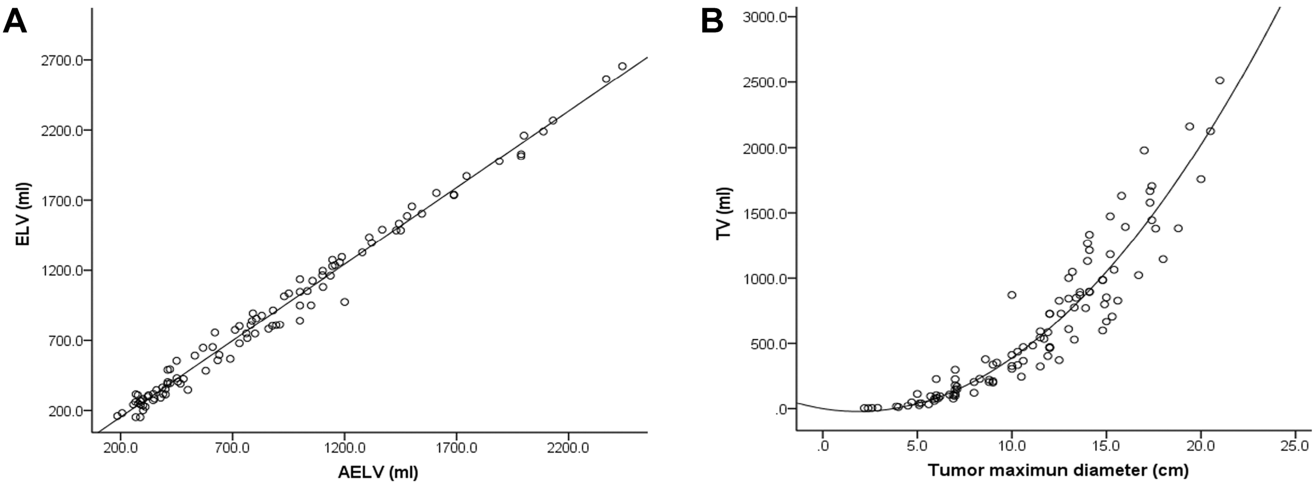

Figure 2. *A. Correlation between simulation predicted ELV and AELV (r=0.994, p<0.001). B. Correlation between maximum tumor diameter and TV (r=0.960, p<0.001). ELV=excised liver volume, AELV=actual excised liver volume, TV=tumor volume.*

3.3. Relative Amount of Excised Volume and Residual Volume

The ratio of EFLV to ELV was negatively correlated with tumor volume (r=-0.823, p<0.001; Figure 3A). ELV/LV, which represented the total resection ratio, was significantly larger than EFLV/FLV, which represented the functional liver resection ratio (55.2±16.8% versus 35.8±14.0%, p<0.001). The average ELV/LV of group A (tumor size ≥ 10 cm) was significantly larger than that of group B (tumor size<10 cm) in both the right hepatectomy and left hepatectomy groups, while the average EFLV/FLV between the two groups was just the opposite (Figures 3B and C). The relative amount of future liver remnant RLV/FLV was significantly larger in group A than that in group B, although the RLV/LV was smaller in group A, and there was no significant difference between the RLV/SLV in the two groups, either in the patients of right hepatectomy or those of left hepatectomy (Figures 3D, E and F).

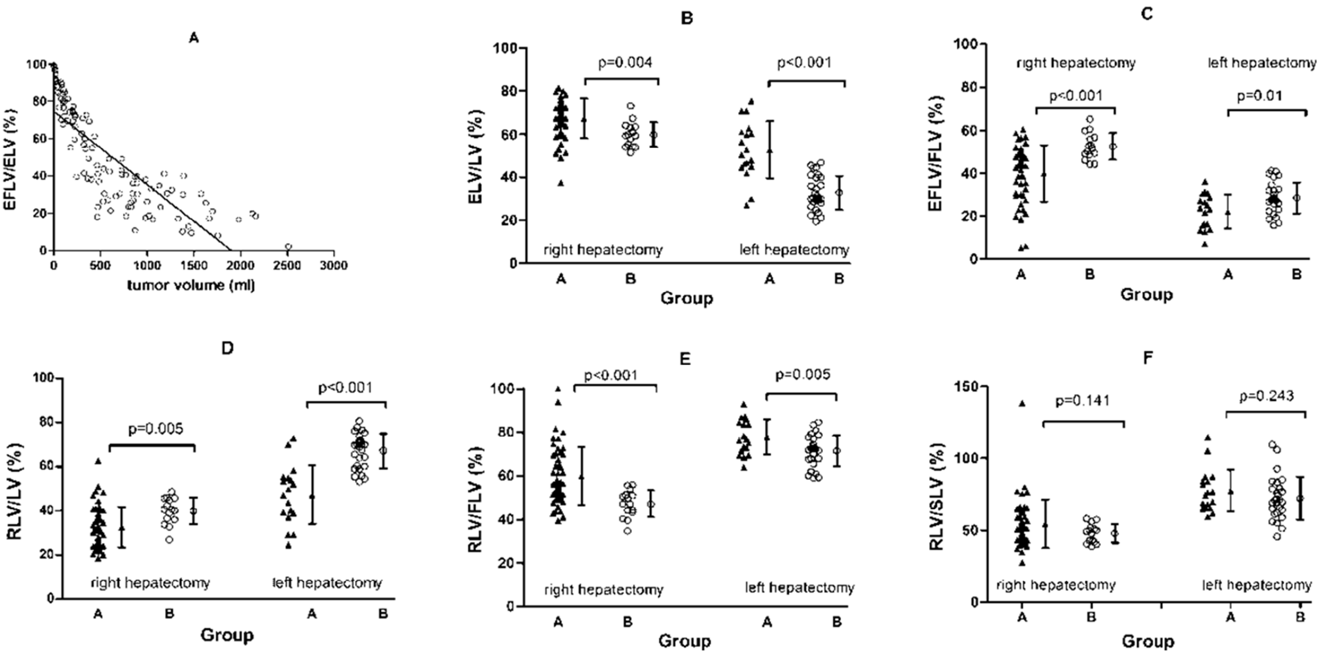

Figure 3. *A. Correlation between tumor volume and functional liver loss to total excision volume (r=-0.823, p<0.001). B and C. Comparison of the total resection ratio as ELV/LV and the functional liver resection ratio as EFLV/FLV between the two groups. D, E and F. Comparison of the relative amount of future liver remnants as RLV/LV, RLV/FLV or RLV/SLV between two groups. LV=liver volume, FLV=functional liver volume, ELV=excised liver volume, EFLV=excised functional liver volume, RLV=residual liver volume, SLV=standard liver volume.*

3.4. Kinetics of Postoperative Liver Function Tests

The kinetics of postoperative liver function tests, such as ALT, PT and SB, are shown in Figure 4. The trends of the kinetics of these three biological markers were similar between group A and group B. Namely, postoperative ALT level was maximum on POD 1 (374±302 versus 331±282 U/L, p=0.465), thereafter deceased progressively reaching to normal on POD 9. Postoperative SB increased until POD 5 (20.5±10.8 versus 23.4±10.4 μmol/L, p=0.246) and thereafter slowly decreased to normal on POD 9. The postoperative PT level peaked on POD 3 (16.6±1.8 versus 16.8±1.9 s, p=0.352), and then decreased progressively reaching a level approximate to normal on POD 9 (15.3±1.2 versus 15.4±1.2 s, p=0.757).

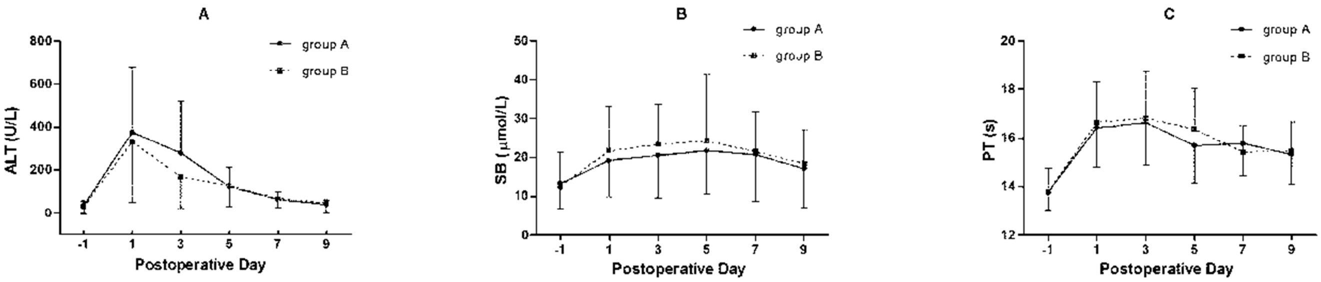

Figure 4. *Similar trend of kinetics of postoperative biologic liver function tests between the two groups. Means±SD of glutamic-pyruvic transaminase (ALT), prothrombin time (PT) and serum total bilirubin (SB) in groups A and B are shown.*

3.5. Distribution of Future Liver Remnant and Postoperative Outcome

RLV/LV ranged from 18.7% to 80.7% with 25 patients having RLV/LV<30%. However, no patients had RLV/FLV<30%, and 105 patients (97.2%) had RLV/FLV>40%. RLV/SLV ranged from 29.7% to 154.2%, with only 1 patient having RLV/SLV<30% and 106 patients (98.1%) having RLV/SLV>40%.

In 60 of 108 (55.6%) patients, one or more complications occurred following liver resection. There were no significant differences in complications such as postoperative liver dysfunction, ascites, pleural effusion, wound infection, or bile leakage between the two groups (Table 1). Nine patients in group A and 2 patients in group B developed postoperative hepatic dysfunction (p=0.246), but no patients died within 30 days of resection due to postoperative liver failure or unrelated causes.

4. Discussion

In oncologic liver surgery, complete tumor removal together with an adequate safety margin and preservation of sufficient liver tissue to maintain liver function are the main concerns [9, 21, 26]. Huge hepatic tumors often press or invade crucial structures, such as major vessels and bile ducts, or are accompanied by cancerous emboli in portal veins or bile ducts. Inappropriate choice of hepatic resection lines may cause unexpected ischemia or venous congestion, prevent residual liver regeneration, and lead to postoperative liver failure [15, 27]. Accordingly, accurate preoperative assessment of liver volume and topography is crucial for safe and curative hepatectomy.

3D reconstruction techniques with preoperative hepatectomy simulation can help make complicated liver resection safe and successful [28, 29]. In this study, we evaluated the reliability and accuracy of 3D reconstruction and hepatectomy simulation for liver resection. 3D reconstruction provided comprehensive and precise anatomical information for the liver, including the positional relationship among the liver, lesions, and vessels, as shown in Figure 1. The accuracy of volumetric assessment was demonstrated by the strong correlation between actual excision volume and predicted excision volume based on hepatectomy simulation of 3D models and the strong correlation between maximum tumor diameter and estimated tumor volume (Figure 2).

Based on this accuracy, we further compared the total liver resection ratio (ELV/LV), functional liver resection ratio (EFLV/FLV), and relative amount of future liver remnant (RLV/LV, RLV/FLV and RLV/SLV) between the two groups of patients with tumor size ≥ 10cm or<10cm (Figure 3). The results indicated that although the excised volume, including the tumor, was large due to hepatectomy in patients with huge hepatic tumors, the amount of normal functional liver lost was limited. In addition, the relative amount of functional residual liver remnant as RLV/FLV was larger in patients with huge hepatic tumors, and RLV/SLV was not different. Therefore, we provided more detailed proof of our previously mentioned clinical observations. Namely, in the same range of anatomical hepatectomy, the larger the tumor was, the less the functional liver tissue would be resected, and the greater the tumor-free residual volume would remain. Therefore, the patients might tolerate the operations well, as the postoperative complications and liver function recovery were similar between the two groups (Table 1 and Figure 4).

This observation might be expected, given the extent of hepatic replacement by large tumors that would not contribute to functional LV. In the case of a large hepatic tumor mass, the contralateral liver segments might have undergone a considerable compensatory hypertrophy, either because this tumor mass does not represent functional liver parenchyma or because it impairs the adjacent portal blood flow, resulting in underestimation of the actual RLV if expressed as a proportion of the total LV [30]. By contrast, in patients with small tumors who require extended resection because of multiple small tumors or centrally located tumors, there is often a lack of hypertrophy of the contralateral liver [31]. Thus, the functional liver resection ratio would not be larger, and future functional liver remnants would not be lower in patients with large tumors who underwent major hepatectomy. For example, the tumor volume of Figure 1A was much larger than that of Figure 1B (1445 ml vs. 227 ml), but EFLV was smaller (211 ml vs. 581 ml), and RLV was similar (561 ml vs. 594 ml). Two other authors also mentioned similar experience in their review articles of hepatic resection [26, 32]. They considered in some situations that a small tumor requires extended hepatectomy, and the risk of postoperative liver failure is higher than that of extended hepatectomy for a large tumor, because a large amount of nontumorous liver is removed.

The results also implied neither ELV nor RLV/LV, but RLV/FLV or RLV/SLV was the better determinant of safety of hepatectomy. Especially in resection for huge hepatic tumors, RLV/LV would underestimate the relative amount of future liver remnant. In our study, 25 of 108 patients had RLV/LV<30%; however the vast majority of the patients had RLV/FLV and RLV/SLV>40%. RLV/FLV and RLV/SLV could exclude the impact of tumor volume, and RLV/SLV could also exclude the impact of body weight and height. Therefore, after excluding the tumor volume, estimating the hepatic functional reserve by the ratio of residual liver volume to functional liver volume or standard liver volume was necessary [11, 30, 33]. It was considered that hepatectomy can be performed safely leaving future liver remnants as much as 20% to 30% in patients with normal liver and exceeding 40% in patients with hepatic cirrhosis [9, 34]. Thus, the ratio here should be RLV/FLV or RLV/SLV rather than RLV/LV.

There were some limitations in this study. Only hemihepatectomy was selected for this study to allow for a close anatomical correlation between the actual surgical resection and simulation procedure. However, a larger extent of hepatectomy might be required for huge hepatic tumors, and nonanatomical hepatectomy might be performed to preserve more normal liver tissue. In this situation, preoperative estimation of future liver remnants (RLV/FLV and RLV/SLV) was also important in ensuring patient safety. Another limitation was that we only focused on the clinical outcome within 30 days of resection. Long term survival might provide more information about the safety assessment of hepatectomy for large hepatic tumor.

5. Conclusion

In conclusion, 3D reconstruction technique could accurately simulate hepatectomy procedure and calculate liver volume. It was helpful to use a 3D reconstruction method for preoperative safety assessment of liver resection for large hepatic tumors in clinical practice. Our results indicated that the amount of normal functional liver lost due to hepatectomy in patients with large liver tumor was limited, although the resected volume, including the tumor, was large. So the patients tolerated the operations well despite the concern of large tumor size. Therefore, another meaningful implication of this study for clinical practice was that neither

ELV nor RLV/LV, but RLV/SLV was the better determinant of safety of hepatectomy.

Abbreviations

3D=three-dimensional, LV=liver volume, SLV=standard liver volume, TV=tumor volume, FLV=functional liver volume, ELV=excised liver volume, EFLV=excised functional liver volume, RLV=residual liver volume, AELV=actual excision liver volume, CT=computer tomography, MDCT=multidetector computed tomography, POD=postoperative days, ALT=Glutamic-pyruvic transaminase, PT=prothrombin time, SB=total serum bilirubin, ICGR15=indocyanine green 15 min retention rate, SD=standard deviation, HBV=hepatitis B virus.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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