Original Article

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Feasibility of novel intraoperative navigation for anatomical liver resection using real-time virtual sonography combined with indocyanine green fluorescent imaging technology

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SUMMARY To analyze the feasibility and clinical effect of novel intraoperative navigation of real-time virtual sonography (RVS) combined with indocyanine green (ICG) fluorescent imaging technology in anatomical liver resection (ALR) for hepatocellular carcinoma. The clinical data of 41 patients who underwent ALR using RVS intraoperative navigation combined with ICG fluorescent imaging technology in the Department of Hepatobiliary Surgery of Peking University International Hospital from January 2020 to May 2022 were retrospectively analyzed. RVS was applied to guide the surgical plane through fusing real-time intraoperative ultrasound images with corresponding preoperative CT or MRI images. Operation methods, operation time, intraoperative blood loss, operative margin, hospital stay and postoperative complications were analyzed. The 1-year overall survival rate and tumor-free survival rate of patients were followed up by outpatient review or telephone calls. ALR surgery was performed on each of 41 patients. There were no deaths during perioperative period and postoperative complications occurred in 7 cases (17.1%). The postoperative pathological examinations demonstrated all cases of hepatocellular carcinoma and negative operative margins. The 41 patients were followed up for 12 to 20 months, with a median follow-up time of 14 months. The overall survival rate 1 year after surgery was 100.0% (41/41), 3 patients (7.3%) experienced tumor recurrence, and the tumor-free survival rate of 1 year after surgery was 92.7% (38/41). In conclusion, novel intraoperative navigation of RVS combined with ICG fluorescent imaging technology is safe and feasible in anatomical segmental hepatectomy of hepatocellular carcinoma.

Keywords hepatocellular carcinoma, hepatectomy, real-time virtual sonography, Indocyanine green

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world, and liver resection is still one of the most effective radical treatments for HCC (*1*). However, the overall prognosis of patients with HCC after surgery is poor, and the rate of 5-year recurrence exceeds 60% (*2*). Due to the characteristics of biological behavior of HCC metastasizing through the portal vein, *Makuuchi* proposed the concept of anatomical liver resection (ALR), which refers to the complete resection of the tumor lesion and the invaded portal vein branches, including the resection of hepatic segment, hepatic subsegment or combined hepatic subsegment with scattered micro-metastasis (*1,3*). Theoretically, ALR is considered to be the most ideal surgical method for the treatment of HCC in terms of tumor eradication, which may reduce the risk of tumor recurrence and improve the overall survival. ALR intends to maximize the benefits with minimal trauma through the surgical operation procedure as well as the perioperative management, and precise intraoperative navigation of the surgical plane is one of the most critical and difficult points while performing the surgery.

The working principle of Indocyanine green (ICG) fluorescent imaging technology is that ICG would bind to the liver parenchymal cells in the body, then the positive staining method which punctures the portal vein of the target liver segment under guidance of intraoperative ultrasound (IOUS) or the negative staining method which ligates the portal vein of the target liver segment and injects it into the peripheral vein are applied, so ALR is able to be performed based on the fluorescent imaging boundary of the area where the portal vein is located (*4*). However, ICG, with its limitations, is applicable only to superficial lesions since it cannot penetrate the deep layer of the liver with its only 5-10mm in depth. Meanwhile it may stain non-target liver segments through communicating blood vessels over time, and lead to the surgical resection plane deviating from the intended plane. Real-time virtual sonography (RVS) technology could simultaneously display real-time IOUS images and corresponding fusion images of real-time IOUS and preoperative CT/MRI side by side on the monitor. Three-dimensional reconstruction software is used to color-mark the target blood vessels and the planned liver resection lines before the surgery, and the RVS system then uses the ultrasound image and the synchronized color CT/MRI fusion image as navigation (*5*). Now RVS has been applied to radiofrequency ablation treatment of liver tumors (*6*) according to a number of literature reviews while currently RVS plus ICG fluorescent imaging technology for ALR have not been reported yet. This study focuses on the application of RVS intraoperative navigation combined with ICG fluorescent imaging technology in ALR, and intends to describe it in detail and to clarify its feasibility and safety.

2. Materials and Methods

2.1. Research subjects

We retrospectively analyzed the clinical data of 41 patients who underwent ALR using RVS intraoperative navigation combined with ICG fluorescent imaging technology at the Department of Hepatobiliary Surgery, Peking University International Hospital from January 2020 to May 2022. Among them, there were 26 males and 15 females, aged (59.8 ± 11.6) years old. The inclusion criteria included: (i) Patients with HCC from a single tumor adopted surgical treatment for the first time; (ii) Upper abdominal contrast-enhanced CT or MRI were performed before the surgery, and RVS intraoperative navigation combined with ICG fluorescent imaging was performed for ALR; (iii) Preoperative assessment of liver function Child-Pugh was in grade A. The exclusion criteria included: (i) Radiotherapy, chemotherapy, interventional therapy and other treatments applied for hepatocellular carcinoma within 4 weeks before the surgery; (ii) Allergy to ICG or iodine; (iii) Preoperative imaging examinations indicating tumor embolus in the main portal vein, common hepatic duct, hepatic vein, or inferior vena cava; (iv) Extrahepatic invasion or metastasis found in the surgery; (v) Organic disease of important organs occurring in heart, lung, kidney, brain, *etc*. This study was approved by the Ethics Committee of Peking University International Hospital and conforms to the provisions of the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from each patient before the surgery.

2.2. RVS system

The RVS intraoperative navigation system is a combination of intraoperative ultrasound and electromagnetic tracking technology (*5,7*), which includes an ultrasound examination system (HI VISION Ascendus, Hitachi, Tokyo, Japan), a convex-type intraoperative ultrasound probe (EUP-O732T, 4.0~10.0 MHz; Hitachi, Tokyo, Japan), an electromagnetic tracker (trakSTAR, Ascension, USA), an electromagnetic generator (Ascension, USA) and electromagnetic sensor (Ascension, USA). An electromagnetic generator was installed on the right front of the patient, and the spatial position of the ultrasound probe was detected using a sterile electromagnetic sensor (Figure 1). A dynamic contrast-enhanced CT or MRI scanning, with a thickness of 1.0 mm, was performed for all patients before the surgery, then CT or MRI images were converted into the format

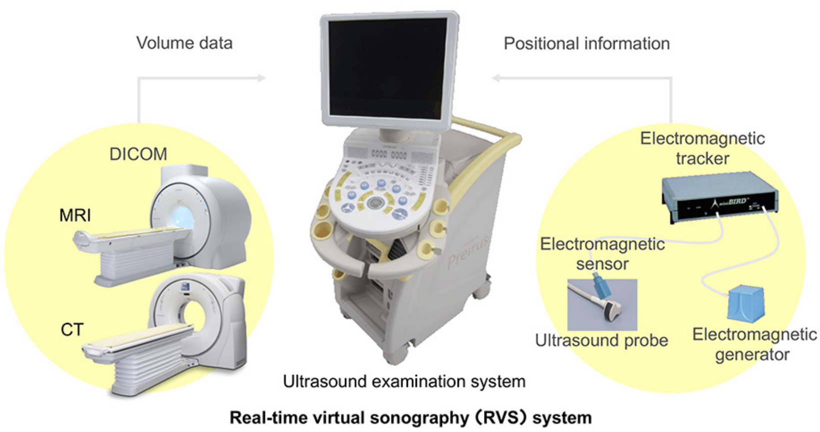

Figure 1. Real-time virtual sonography (RVS) system, including ultrasound examination system, ultrasound probe, electromagnetic tracker, electromagnetic generator and electromagnetic sensor.

of digital imaging and communications in medicine (DICOM), and three-dimensional reconstruction was done through 3D simulation software (Toshiba, Tokyo, Japan) while the data of liver parenchyma, liver vessels and tumors were extracted. The DICOM data were then input into the RVS system.

2.3. Procedure

The round ligament and the falciform ligament of liver are incised after performing an exploratory laparotomy. RVS system then is started and adjusted according to the following procedure: (i) selecting the CT image of the sagittal part of the portal vein, display and fix it on the left side of the RVS screen; (ii) selecting the IOUS image about the same location as the left image, and display it on the right side of the RVS screen, pressing the start button to synchronize the left and right images. At this point, the synchronization of images is a rough match only, and the complete matching requires another two intrahepatic anatomical points to conduct image synchronization; (iii) selecting the hepatic vein or portal vein branches near the tumor and the tumor center as anatomical points to conduct image synchronizations as specified above until the hepatic vein or portal vein branches near the tumor are matched accurately (Figure 2).

2.4. Surgical operation

After the accurate spatial position registration, the liver is kept in a relatively stable position, RVS intraoperative navigation combined with ICG fluorescent imaging technology is then applied to determine the boundaries of surgical resection of liver segments or subsegments, and the resection line is marked with electrotome. The liver parenchyma is dissected by Pringle and clamp technique. During the process of liver segments resection, the resection plane is observed intermittently by RVS to verify its correctness and to confirm the adequate surgical margins and preservation of key vessels (Figure 3).

2.5. Observation indicators

Observation indicators include the operation method, operation time, intraoperative blood loss, location of tumor, pathological results, surgical margins, hospital stay, postoperative complications, and application of RVS intraoperative navigation combined with ICG fluorescent imaging technology during the operation. Postoperative complications were graded by the Clavien-Dindo system (*8*). The one-year overall survival rate and tumor-free survival rate of the patients were followed up by outpatient review or telephone calls with the follow-up deadline as of May 2023.

2.6. Statistical analysis

SPSS 22.0 (SPSS, Chicago, IL) was used for data processing. The measurement data conforming to the normal distribution is represented as the mean ± standard error and the measurement data conforming to the non-normal distribution is represented as median with range.

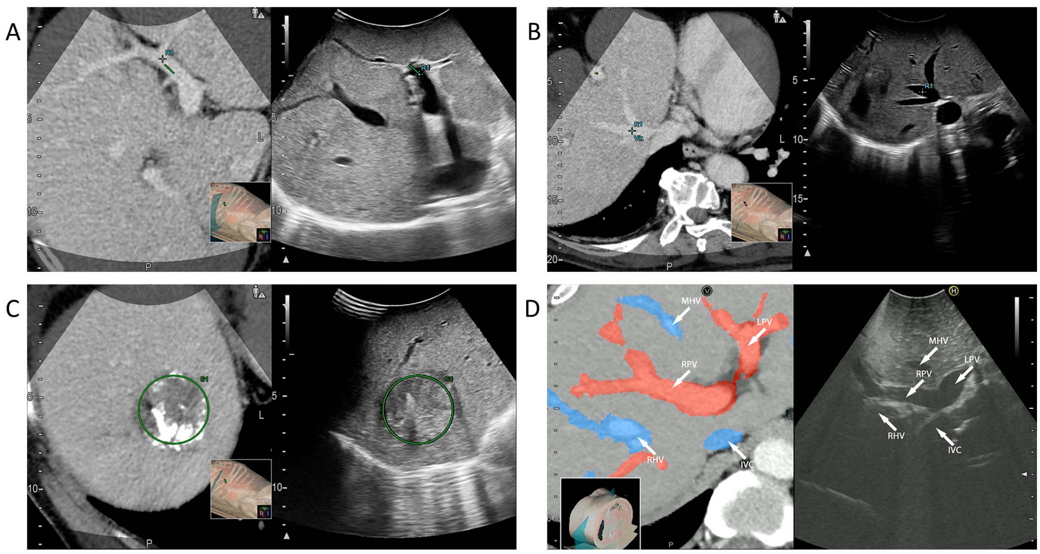

Figure 2. The adjusting procedure of real-time virtual sonography (RVS) system. (A) Adjust and match the CT image of the sagittal part of the portal vein (R1 in left image) and the intraoperative ultrasound image (R1 in right image). **(B)** Adjust and match the CT image of the middle hepatic vein (R1 in left image) and the intraoperative ultrasound image (R1 in right image). **(C)** Adjust and match the CT image of the tumor (S1 in left image) and the intraoperative ultrasound image (S1 in right image). **(D)** The fusion image (left image) and the intraoperative ultrasound image (right image) were observed after adjusting and matching procedure. Right hepatic vein (RHV), middle hepatic vein (MHV), left hepatic vein (LHV), right portal vein (RPV), left portal vein (LPV) and inferior vena cava (IVC) were marked with white arrows.

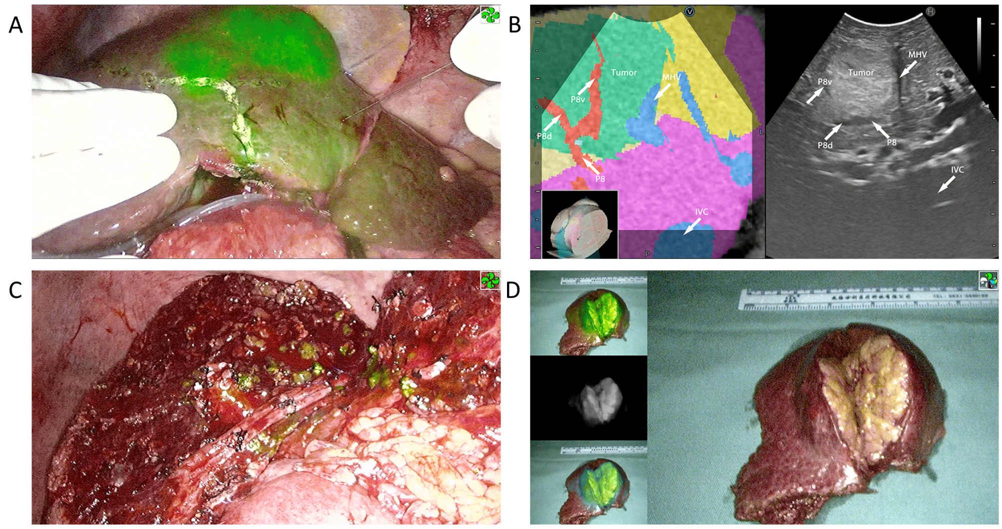

Figure 3. Anatomical liver resection (ALR) of segments 8 and 4b was performed by real-time virtual sonography (RVS) combined with indocyanine green (ICG) fluorescent imaging technology. (A) Fluorescent staining of segment 8 and segment 4b of liver. **(B)** The fusion image (left image) and the intraoperative ultrasound image (right image) were observed in RVS system. Tumor was marked with green in the left image. Middle hepatic vein (MHV), portal vein of segment 8 (P8), dorsal branch of portal vein of segment 8 (P8d), ventral branch of portal vein of segment 8 (P8v), and inferior vena cava (IVC) were marked with white arrows. **(C)** The resection plane of liver. **(D)** Frontal view of the specimen.

3. Results

3.1. Clinical characteristics of included patients

The clinical characteristics of included patients are summarized in Table 1. According to ECOG (Eastern Cooperative Oncology Group) performance status, 39 patients (95.1%) scored 0 and 2 patients (4.9%) scored 1 out of 41 patients. The 15-minute retention rate of ICG for each patient was less than 10% and all patients were classified as stage I in accordance with China liver cancer staging (CNLC). All 41 patients had open surgery of ALR.

Table 1. Patients' baseline and clinical characteristics

Parameters	Total (n = 41)
Age, years (median, IQR)	61 (50–66)
< 60	18 (43.9%)
≥ 60	23 (56.1%)
Sex, n (%)	
Female	15 (36.6)
Male	26 (63.4)
ECOG performance, n (%)	
0	39 (95.1)
1	2 (4.9)
Child-Pugh score, n (%)	
A	40 (97.6)
B	1 (2.4)
ICGR-15, % (median, IQR)	5.6 (4.0–7.0)
HBV infection, n (%)	
Positive	38 (92.7)
Negative	3 (7.3)
AFP, ng/mL (median, IQR)	73.5 (2.9–755.2)
< 20	19 (46.3)
≥ 20	22 (53.7)
CNLC stage, n (%)	
Ia	32 (78.0)
Ib	9 (22.0)
Tumor diameter, cm (median, IQR)	4.0 (2.4–5.0)

Abbreviation: AFP, alpha fetal protein; CNLC, China liver cancer staging; ECOG, Eastern Cooperative Oncology Group; ICGR, indocyanine green rate; IQR, inter quartile range.

3.2. Information of anatomic hepatic segmentectomy

The surgical procedures of patients are summarized in Table 2. Among them, there was 1 case of segment II resection (2.4%), 1 case of segment III resection (2.4%), 4 cases of segment IV resection (9.8%), 5 cases of segment V resection (12.2%), 10 cases of segment VI resection (24.4%), 7 cases of segment VII resection (17.1%), 6 cases of segment VIII resection (14.6%), 1 case of segments IVb+VIII resection (2.4%), and 1 case of segments V+VIII resection (2.4%). The perioperative outcomes of patients are shown in Table 3. The operation time of 41 patients was (417.3 ±123.1) min, the intraoperative blood loss was 390.0 (250.0, 500.0) ml, and 5 cases (12.2%) received intraoperative blood transfusions. The hospital stay of 41 patients was (15.1 ± 2.9) days. No perioperative deaths occurred. Postoperative complications occurred in 7 cases (17.1%), of which 4 cases (9.8%) were ascites, 1 case (2.4%) was incision infection in Clavien-Dindo grade I, 1 case (2.4%) was postoperative bleeding, and 1 case (2.4%) was pulmonary infection in Clavien-Dindo grade II. Postoperative pathological examinations indicated hepatocellular carcinoma, including 6 cases (14.6%) of Edmondson-Steiner grade I, 24 cases (58.5%) of grade II, and 11 cases (26.8%) of grade III, and the surgical

Table 2. The operative procedures of patients

Operative procedure	Total (*n* = 41)
Segmentectomy, *n* (%)	
S2	1 (2.4)
S3	1 (2.4)
S4	4 (9.8)
S5	5 (12.2)
S6	10 (24.4)
S7	7 (17.1)
S8	6 (14.6)
Multisegmentectomy, *n* (%)	
S4b+8	1 (2.4)
S5+8	1 (2.4)
Hemihepatectomy, *n* (%)	
S2+3+4	3 (7.3)
S5+6+7+8	2 (4.9)

Abbreviation: S, segment, defined by Couinaud's nomenclature.

Table 3. The perioperative outcomes of patients

Perioperative outcomes	Patients (*n* = 41)
Intraoperative outcomes	
Operation time, min (median, IQR)	400.0 (345.0–450.0)
Pringle time, min (median, IQR)	30.0 (25.0–45.0)
Operative blood loss, mL (median, IQR)	390.0 (250.0–500.0)
Intraoperative blood transfusion, *n* (%)	5 (12.2)
Negative resection margin, *n* (%)	41 (100.0)
Postoperative results	
Postoperative hospital stay, days (median, IQR)	14.0 (10.0–19.0)
90-day mortality, *n* (%)	0
R0 resection, *n* (%)	41 (100.0)
Hepatocellular carcinoma, *n* (%)	41 (100.0)
Microvascular invasion, *n* (%)	22 (53.7)
Edmondson-Steiner grade, *n* (%)	
I	6 (14.6)
II	24 (58.5)
III	11 (26.8)
IV	0
Cases of recurrence, *n* (%)	3 (7.3)
The 1-year overall survival, *n* (%)	41 (100.0)
The 1-year disease-free survival, *n* (%)	38 (92.7)
Type of complications	
Postoperative hemorrhage, *n* (%)	1 (2.4)
Incision infection, *n* (%)	1 (2.4)
Seroperitoneum, *n* (%)	4 (9.8)
Lung infection, *n* (%)	1 (2.4)
Clavien-Dindo Classification, *n* (%)	
I	5 (12.2)
II	2 (4.9)
III	0
IV	0

Abbreviation: IQR, inter quartile range.

margins of all patients were negative. 41 patients were followed up for 14 to 22 months, with a median follow-up time of 14 months. The overall survival rate of 1 year after surgery was 100.0% (41/41). There were 3 patients (7.3%) with tumor recurrence after the surgery, and the tumor-free survival rate of 1 year after surgery was 92.7% (38/41).

3.3. Safety and feasibility

(i) *Intraoperative situation*: RVS intraoperative navigation combined with ICG fluorescent imaging technology does not interfere with the surrounding environment, and is able to guide the puncture of portal vein of liver segment and the operation plane of segmental hepatectomy accurately. The resection plane under RVS navigation was consistent with that of the preoperative plan in each case. (ii) *Postoperative situation*: there were 7 patients (17.1%) with postoperative complications. According to the Clavien-Dindo system classification, 5 cases (12.2%) were in grade I, 2 cases (4.9%) were in grade II and no perioperative death occurred. It is safe and feasible to apply RVS intraoperative navigation combined with ICG fluorescent imaging technology in ALR.

4. Discussion

In 1985, Makuuchi *et al*. (*9-11*) proposed the concept of ALR including anatomic segmental and subsegmental liver resections based on the theory of Couinaud's liver segment. Makuuchi is the first to put forward the IOUS for surgery of ALR, and also to practice liver segmental staining, dissection of glisson's sheath (extrathecal dissection and intrathecal dissection) and other surgical methods, which then created an era of precise liver resection.

HCC tends to metastasize along the portal vein in the liver segments where the tumor is located (*12*). ALR not only removes the tumor but also removes the liver segment of the portal vein branch where the tumor is located, which can reduce the risk of metastasis (*13*). The theory of tumor blood flow drainage proposed by Sakon *et al*. (*14*) also demonstrated that the recurrence of liver cancer is the direct spread of tumor through portal vein blood flow. Retrospective studies have also been reported that anatomic hepatectomy reduces the risk of recurrence of local tumor and has a better prognosis than non-anatomic hepatectomy (*2,15*).

In anatomic hepatectomy, it is crucial to determine the surgical resection plane. Traditional ALR mainly relies on blocking the portal vein of the target liver segment to display the ischemic line on the liver surface, and exposing the hepatic veins throughout the entire operation under IOUS to determine the surgical resection plane. However, due to the irregular boundaries between the liver segments and the variation of intrahepatic vessels, the plane of hepatectomy and the extent of resection are often not accurate enough during the liver resection. Staining with ethylene blue can be used to assist in judging the plane of hepatectomy, but with shortcomings including short imaging time, unclear field of view, and rapid clearance. ICG has been widely used in cholangiography and tests of reserved liver function, and has been gradually applied in anatomic hepatectomy (*16*). ICG fluorescent imaging technology can display the resection range of liver segments and tumor boundaries, which allows for a more accurate anatomic hepatectomy (*17*). Nevertheless, ICG fluorescent imaging technology also has certain limitations: (i) Fluorescent signal interference: ICG can diffuse through the rami communicantes between liver segments, thus affects the judgment of the surgical resection plane; (ii) Poor imaging of deep tumors: since the fluorescent signal of ICG can only penetrate 5-10 mm of liver tissue, ICG usually does not provide enough image for deep tumors (*18*).

RVS fuses the images of ultrasound and CT/MRI, and thus is able to combine the good spatial resolution of CT/MRI with the advantages of real-time dynamic observation of ultrasound (*19*). Adopting the method of spatial magnetic positioning, RVS is able to achieve real-time correspondence between ultrasound images and CT/MRI images through image position registration, and then the IOUS and fusion images are simultaneously displayed on the RVS operation interface (*20*). On the basis of image fusion, the RVS system uses the electromagnetic sensor fixed on the ultrasound probe and the electromagnetic generator of the navigation system to precisely match the image of ultrasound with CT/MRI to realize free tracking of spatial positioning. It can make any section displayed on the same screen or fused in real time, simulate the scope and plane of liver resection, identify the location of the tumor and its surrounding duct structure during the surgery to guide the plane of liver resection in real time for performing ALR.

Studies have shown that RVS's ability to distinguish liver cancer from surrounding normal tissues is better than IOUS, with a better detection rate for small lesions (*21*). RVS can use different colors to mark the simulated images of liver tumors, portal veins, hepatic veins, and normal liver tissues, and determine the tumor boundary which cannot be clearly distinguished by IOUS, to guide the resection plane in real time through the fusion images (*22*). Real-time navigation of RVS during the surgery makes up for limitations of ICG fluorescent imaging, and most importantly, it is a bridge between preoperative CT/MRI and IOUS which helps the surgeons in planning and adjusting the optimal surgical plan during the surgery.

There are two main issues concerned when using the RVS systems: (i) whether the initial position markers remained accurate; and (ii) whether the position registration procedure is too complex and time-consuming. The accuracy of position registration is the foundation of the RVS system, without it, RVS cannot perform accurate surgical navigation. Surgical operations easily lead to changes in the position and shape of the liver, which makes it more difficult for RVS to match the scanning planes of CT/MRI and IOUS during surgery, and it is almost impossible to intraoperatively register the position of the entire liver. Nevertheless, the target area for ALR is usually limited to within the liver segments or to an area around the tumor, so it is not necessary to record the entire liver but only the location near the target area with acceptable accuracy. According to our experience, we suggest the following points that are helpful in position registration: (i) The electromagnetic generator should be placed as close as possible to the operating bed (20–70 cm), otherwise the registration accuracy may be affected; (ii) Appropriate intraoperative detection points of IOUS need to be selected. The detection point of ultrasound must be set on the liver surface when conducting the intraoperative scanning. We prefer to choose the round ligament of the liver, which is easy to be identified and of which the position is fixed; (iii) Portal vein branches or hepatic veins near the tumor are recommended as important landmarks; (iv) For more precise adjustment, it is recommended to select the tumor center as the marking point and accurately match the direction and angle of the hepatic vein or portal vein near the tumor. The accuracy of position matching can be maximized through the above practices, thereby obtaining accuracy of image matching. It is noted that accurate image matching is not a simple process, and the time for spatial position registration could be significantly reduced with improvement of operating proficiency and skills, to achieve satisfactory accuracy.

However, the RVS system also has some limitations. First, the magnetic field is susceptible to bending by magnetic materials during the surgery. Therefore, magnetic materials should not be placed between the electromagnetic sensor and the electromagnetic generator, medical tweezers, scissors, metal tractors and other magnetic materials should be placed 5~10 cm away from the electromagnetic sensor. Second, with the development of laparoscopic technology, liver surgery tends to gradually become minimally invasive, RVS has yet to be used in laparoscopy, and it is expected that an update of equipment or devices will enable RVS to be used in laparoscopic anatomic hepatectomy in the future.

For this study, there are some limitations because it is an exploratory study without a control group, and may affect the credibility of the conclusion. Thus, prospective randomized controlled trials may need to be carried out for the sake of a high grade of evidence.

We evaluated the safety and feasibility of RVS intraoperative navigation combined with ICG fluorescent imaging technology for hepatectomy in our study. This novel intraoperative navigation uses ICG fluorescence imaging to determine the surface boundary of hepatectomy while the plane of liver resection can be modified in real time through RVS to make up for the shortcomings of ICG fluorescence imaging, thus helping to determine a clear route of hepatectomy, reducing intraoperative bleeding and preserving the normal liver parenchyma to the greatest extent, so as to achieve the goal of anatomic segments or subsegments hepatectomy.

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