Virtual Liver Resection and Volumetric Analysis of the Future Liver Remnant using Open Source Image Processing Software

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Abstract

Background After extended liver resection, a remnant liver that is too small can lead to postresection liver failure. To reduce this risk, preoperative evaluation of the future liver remnant volume (FLRV) is critical. The open-source OsiriX® PAC software system can be downloaded for free and used by nonradiologists to calculate liver volume using a stand-alone Apple computer. The purpose of this study was to assess the accuracy of OsiriX® CT volumetry for predicting liver resection volume and FLVR in patients undergoing partial hepatectomy.

Methods Preoperative contrast-enhanced liver CT scans of patients who underwent partial hepatectomy were analyzed by three observers. Two surgical trainees measured the total liver volume, resection volume, and tumor volume using OsiriX®, and a radiologist measured these volumes using CT scanner-linked Aquarius iNtuition® software. Resection volume was correlated with prospectively determined resection weight, and differences in the measured liver volumes were analyzed. Interobserver variability was assessed using Bland–Altman plots.

Results 25 patients (M/F ratio: 13/12) with a median age of 61 (range, 34–77) years were included. There were significant correlations between the weight and volume of the resected specimens (Pearson's correlation coefficient: $R^2 = 0.95$). There were no major differences in total liver volumes, resection volumes, or tumor volumes for observers 1, 2, and 3. Bland–Altman plots showed a small interobserver variability. The mean time to complete liver volumetry for one patient using OsiriX® was 19 ± 3 min.

Conclusions OsiriX® liver volumetry performed by surgeons is an accurate and time-efficient method for predicting resection volume and FLRV.

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Currently the focus of liver resection criteria is principally the limited functional reserve of liver tissue that remains after resection. Extended resection, staged resection, preoperative portal vein embolization to increase future remnant liver volume, and resection combined with tumor ablation is becoming standard in specialized liver units worldwide. More preoperative chemotherapy is being used in parallel with these aggressive strategies; as a consequence, more complicated and extended resections are being performed with reduced residual parenchymal function and smaller remnant livers [1].

Schindl et al. reported that partial liver resection can only be performed safely if the remnant liver volume is

more than 26.6% of the total functional liver volume in patients with normal liver parenchyma [2]. The safe margin increases to 40% in patients with high-grade steatosis and after oxaliplatin- or irinotecan-based neoadjuvant chemotherapy, and the safe margins are >50% of the total liver volume for cirrhotic livers [2, 3].

Both a small postoperative remnant liver size and an inappropriately functioning liver parenchyma increase the risk of postresectional liver failure (PLF) [2, 4, 5]. Preoperative assessment of future remnant liver volume and liver function is imperative to reduce this risk. Although accurate prediction of postresectional liver function remains difficult, there are a variety of tests used to asses this [6–10]. For example, the 15-minute indocyanine green retention test (ICG R15) measures the clearance capacity of the liver and is probably the most commonly used test in patients who undergo liver resection. To determine the maximum possible extent for safe liver resection, Makuuchi et al. and Clavien et al. proposed the use of decision trees that incorporate the ICG R15 [11, 12]. More recently, the ^{13}C-methacetin LiMAx breath test has been proposed for assessing hepatic functional capacity [13].

A number of studies have validated tools to determine liver volume, with a particular focus on the volume of the future remnant liver. Computed tomography (CT) or magnetic resonance imaging (MRI) volumetry can be used to accurately predict total liver volume and future remnant liver volume [14–16]. Usually specialized hepatic radiologists perform the volumetric assessments using commercial software linked to radiological hardware. However, hepatic volumetry also can be performed accurately by a nonradiologist on a personal computer using open source ImageJ® provided by the National Institutes of Health [15]. Recently, a more user-friendly, freely downloadable open source image analysis software package, OsiriX®, has become available. This software for Apple Mac OS has not yet been validated for liver CT volumetry. The purpose of this study was to assess the accuracy of OsiriX® in performing liver CT volumetry by surgeons using personal computers and to compare the results to liver CT volumetry performed by a radiologist using classical radiological software (iNtuition®) linked to a CT-scanner system.

Patients and methods

A database of patients undergoing liver resection in Maastricht University Medical Centre (Maastricht, The Netherlands) was created in 2000. Data of all patients were collected prospectively from 2000 onwards. From this database, all patients who underwent resection of two or more liver segments for primary or secondary liver tumors were selected if the resection specimen weight had been obtained in the operating room directly after resection ($n = 110$). From this group, the 25 most recently treated patients were selected and included for volumetric analysis. All resection specimens were postoperatively assessed by an experienced pathologist.

CT volumetry

Portal venous phase series of images from the preoperative contrast-enhanced CT scans were used for CT volumetry. Two observers (JV and IH, both house officers; observers 1 and 2, respectively) performed liver volumetry for all 25 patients on an iMac using OsiriX®. Both observers were medical students in their final year of medical school who were trained in liver anatomy and the use of OsiriX® by one of the liver surgeons (RD). A specialized liver radiologist (RS: observer 3) performed liver volumetry on exactly the same scans using iNtuition® (TeraRecon, Houston, TX). iNtuition® is the standard commercially available image analysis software package used in our liver unit. Total liver volume, resection volume, and tumor volume were determined using OsiriX® (observers 1 and 2) or iNtuition® (observer 3). Observers were blinded to the prospectively collected resection weights and to each other's results. On all slices, the gall bladder and the inferior caval vein were excluded in the regions of interest, and the intrahepatic vascular and biliary structures were included. For patients who underwent a hemihepatectomy, the transection line of the virtual liver resection followed Cantlie's line from the top of the gallbladder, paralleling the middle hepatic vein straight to the suprahepatic inferior caval vein. The middle hepatic vein was excluded from the virtual resection. Extended or extra-anatomic resections were guided by the operation notes. The total time required to perform liver volumetry was measured for all three observers.

Calculation of liver volume with OsiriX®

Downloading OsiriX®

The 32-bit OsiriX® version 3.3 was downloaded from: http://www.osirix-viewer.com under the dropdown menu "downloads." A 2.8-Ghz Intel Core 2 Duo 24" iMac (Apple Inc., Cupertino, CA, USA) was used.

Loading a series of images into OsiriX®

After inserting a CD-ROM or DVD containing CT scan data (including a commercial viewer), the "Digital Imaging and Communications in Medicine" (DICOM) data were automatically extracted from the disc by OsiriX® and imported into the OsiriX® viewer (Fig. 1a).
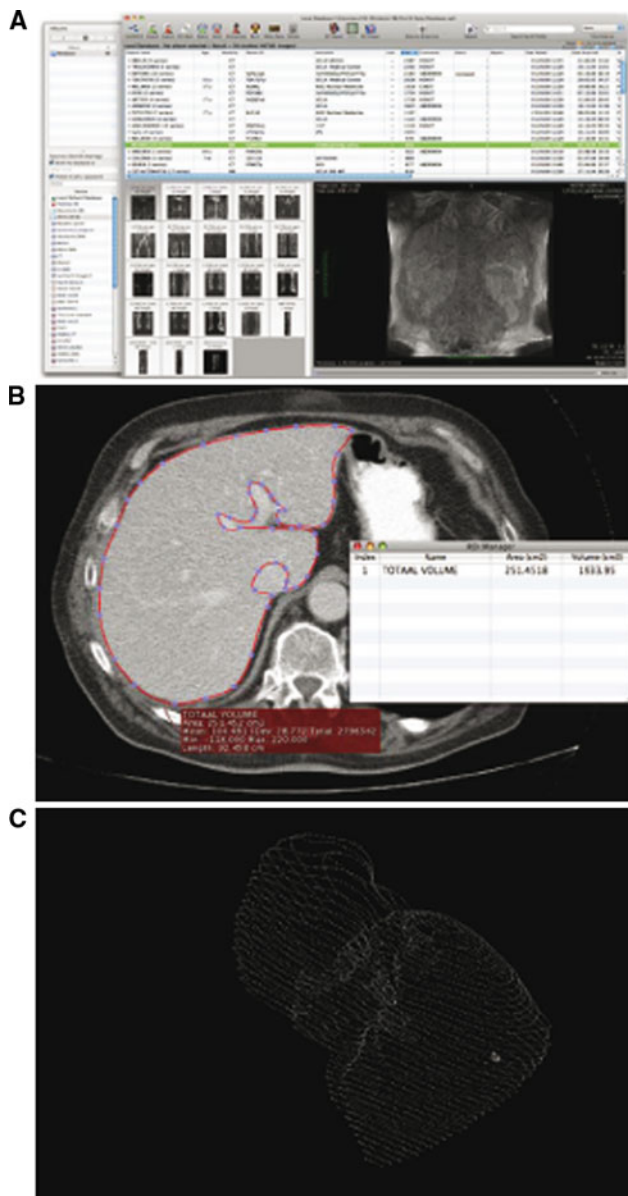
Fig. 1 **a** Picture archiving and communication system integrated in Osirix Software package. **b** Outlining liver tissue. **c** 3D liver image

Storing DICOM data in the OsiriX® "picture archiving and communication system" (PACS)

DICOM data were stored in the OsiriX® PACS using the "Copy linked files to Database folder" under "file" in the OsiriX® dropdown menu.

Contouring the liver and generating regions of interest

Volumetry was performed on sets of axial images in the portal venous phase using a slice thickness of 3–5 mm. As a consequence of using CD-ROM containing DICOM CT scan data of referring centers, the slice thickness varied.

Three kinds of volumetric assessments were performed prospectively in this study: total liver volume, resection volume, and tumor volume. The outline of the future resection specimen was traced manually on each slice with the "closed polygon selection" tool under the ROI tool button using a pen tablet system (Intuos 3, Wacom Co ltd., Saitama, Japan). The "Grow Region (2D/3D Segmentation)" tool in the "ROI" dropdown menu made it possible to automatically outline the total liver and the metastases. This modality of OsiriX® is based on the differences in Hounsfield units between the liver parenchyma, bony structures, and body fat. The automatic outlines are hand-adjusted with the "closed polygon selection" tool and "repulsor tool" to optimize the ROI (Fig. 1b).

Calculating actual liver volumes

After selecting all of the regions of interest within one series, OsiriX® automatically calculated the volume by multiplying surface and slice thickness and then adding up individual slice volumes. OsiriX® also provided 3D images using the "ROI volume" tool (Fig. 1c).

Statistical analysis

Actual resection weights obtained in the operating room were taken as the reference standard for CT volumetric resection measurements for both modalities. The volumes measured by the specialized radiologist using iNtuition® were assumed to be the reference standard to validate OsiriX®. Total liver volume, resection volume, and tumor volume were reported. The percentage of functional remnant liver volume (compared with the total functional volume) was calculated (FRLV%). Unless otherwise stated, data are presented as the mean volume ± standard deviation. Pearson's correlation coefficient R^2 was used to test correlations between resection specimen weight and measured CT volumes using OsiriX®. The mean differences between observers 1, 2, and 3 were tested with one-way ANOVA and paired t tests corrected using the Bonferroni correction. Interobserver agreement was assessed with Bland–Altman plots. For total volume, resection volume, tumor volume, and FRLV%, the average was plotted against the difference and 95% limits of agreement were provided. P values <0.05 were considered significant. Statistical analysis was performed using GraphPad Prism software (version 5.01; California, USA).

Bland–Altman plots were used to assess intraobserver variability between OsiriX® and iNtuition® (observers 1 and 3) and between two observers using OsiriX® (observers 1 and 2). For total volume, resection volume, tumor volume, and functional remnant liver volume

percentages, the average was plotted against the difference and 95% limits of agreement were provided.

Results

Patients

Twenty-five patients who underwent liver resection for colorectal cancer liver metastases were included in this study (Table 1). Five of 25 patients (20%) were treated preoperatively with chemotherapy. Microscopic examination of the resection specimens revealed minor steatohepatitis in one of the patients. The liver parenchyma was normal in all others.

Specimen volume and resection specimen weight

For observers 1, 2, and 3, resection volumes assessed by OsiriX® or iNtuition® volumetry correlated strongly with actual resection weights obtained in the operating room immediately after resection (R^2 = 0.95, 0.94, and 0.95, respectively; Fig. 2). The resection weight-to-volume ratio measured by OsiriX® was 0.85, 0.86, and 0.91 g/ml for observers 1, 2, and 3, respectively.

CT liver volumes

The FRLV% was calculated, and all volumes were plotted for each observer (Fig. 3). For the mean total liver volume, no significant differences were found between observer 1 (1740 ml ± 471.6), observer 2 (1722 ml ± 466.3), and observer 3 (1683 ml ± 460.8). For the mean resection volume, no significant differences were found between observer 1 (956 ml ± 462.7), observer 2 (965 ml ± 474.2), and observer 3 (918 ml ± 461.9). There also were no significant differences found for the mean tumor volume measured by observer 1 (84.58 ml ± 208.5), observer 2 (79.03 ml ± 182.7), and observer 3 (86.31 ml ± 215.3). Finally, no significant differences were found in the mean FRLV% for
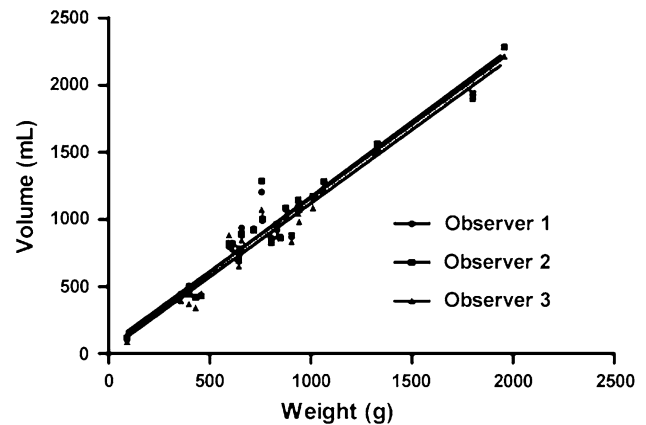
Fig. 2 Actual resection weight measured in the operating room directly after resection is plotted against the estimated resection volume by observers 1, 2, and 3

observer 1 (46.27% ± 17.86), observer 2 (45.4% ± 18.5), and observer 3 (46.78% ± 18.35).

Intraobserver variability

Liver volumetry measurements were compared using Bland–Altman plots, and the 95% limits of agreement were calculated (Figs. 4 and 5).

Efficiency

The mean time needed to perform complete volumetry in a patient (total liver volume, resection volume, and tumor volume) was 19 ± 3 min when a 5-mm scan slice thickness was used.

Discussion

Accurate preoperative risk assessment to determine whether a patient can undergo major or extended liver resection remains the Holy Grail of liver surgery. In so far as volume equates to function, assessment of liver volume, and particularly the volume of the liver remnant, is critical. Unfortunately, liver volumetry is not always available, because it is usually linked to the CT scanner system and requires an experienced radiologist. User-friendly and easily accessible instruments are needed to predict remnant liver volume and parenchyma quality. OsiriX® is an open source image analysis package and PAC system that can be downloaded free of charge. The goal of this study was to validate OsiriX for liver volumetry. The accuracy and efficiency of OsiriX® for measuring liver volumes in patients undergoing partial liver resection was analyzed and compared with actual resection weights and CT liver

Table 1 Patient characteristics

Parameter	Results
Age, year (range)	61 (34–77)
Male/female ratio	13/12
Right hepatectomy	14
Right hepatectomy + metastasectomy	5
Left hepatectomy	1
Left hepatectomy + metastasectomy	1
Extended right hepatectomy	1
Left lateral hepatic sectionectomy	3

Fig. 3 a Mean total liver volume is plotted for observers 1, 2, and 3. Horizontal lines represent mean ± SD. No significant differences were found. **b** Mean resection volume is plotted for observers 1, 2, and 3. Horizontal lines represent mean ± SD. No significant differences were found. **c** Mean metastases volume is plotted for observers 1, 2, and 3. Horizontal lines represent mean ± SD. No significant differences were found. **d** Mean functional remnant liver volume as a percentage of total functional liver volume is plotted for observers 1, 2, and 3. Horizontal lines represent mean ± SD. No significant differences were found
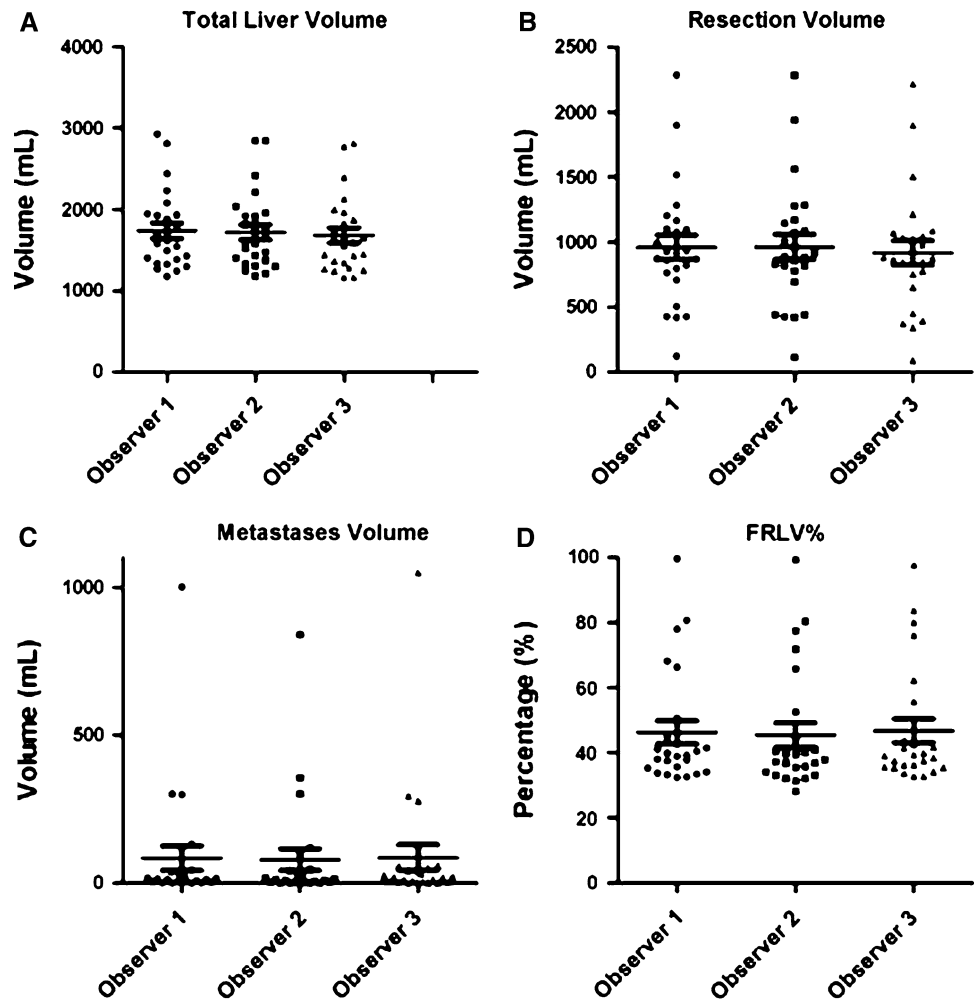
volumetry using iNtuition® software linked to the CT scanner system; the latter is currently the clinical standard at the Maastricht University Medical Centre.

In this study, we found a strong and highly significant correlation between resection weight and resection volume measured with OsiriX® and iNtuition® (Fig. 2). The mean resection weight-to-volume ratio calculated with OsiriX® was 0.85 ± 0.11 for observer 1, 0.86 ± 0.11 g/ml for observer 2, and 0.91 ± 0.13 g/ml for observer 3. These ratios and the systematic overestimation of the liver volume were in accordance with previous studies [14, 15]. A volumetric assessment of fully perfused livers compared with the weight of a resection specimen in a nonperfused state in the operating room could explain the systematic overestimation of liver volume. This, however, will not affect the functional remnant liver volume as a percentage of the total functional liver volume, which Schindl et al. reported to be an important determinant of the risk for developing postoperative liver failure [2].

To validate the OsiriX® software package, volumetric assessments performed with OsiriX® were compared with

those performed with iNtuition®. In addition, we compared the volumes measured by the two observers using OsiriX®. One-way ANOVA and *paired t* tests showed that there were no significant differences in the mean volumes calculated with OsiriX® and iNtuition® or between the two observers using OsiriX®. This means that trained surgical trainees using OsiriX® for liver CT volumetry perform equally well as specialized radiologists using iNtuition®.

Although there were no significant differences in the mean volumes, the results of the two software packages at the individual patient level revealed some differences that must be noted. The differences in measured volumes at the individual patient level can be clarified using Bland–Altman plots (Figs. 4 and 5) and become particularly important in extended resections. In cases in which the preoperative liver volume assessment shows that the reported functional remnant liver volume percentage approaches 26.6%, extra care is recommended.

The measured volumes were consistently overestimated using iNtuition®. In this study, we discovered that volumes calculated by iNtuition® are inexplicably altered when the

Fig. 4 **a** Mean total volume of observers 1 and 2 is plotted against the difference in total volume between observers 1 and 2. **b** Mean resection volume of observers 1 and 2 is plotted against the difference in resection volume between observers 1 and 2. **c** Mean metastases volume of observers 1 and 2 is plotted against the difference in metastases volume between observers 1 and 2 **d**. Mean functional remnant liver volume as a percentage of total functional liver volume of observers 1 and 2 is plotted against the difference in functional remnant liver volume as a percentage of total functional liver volume between observers 1 and 2
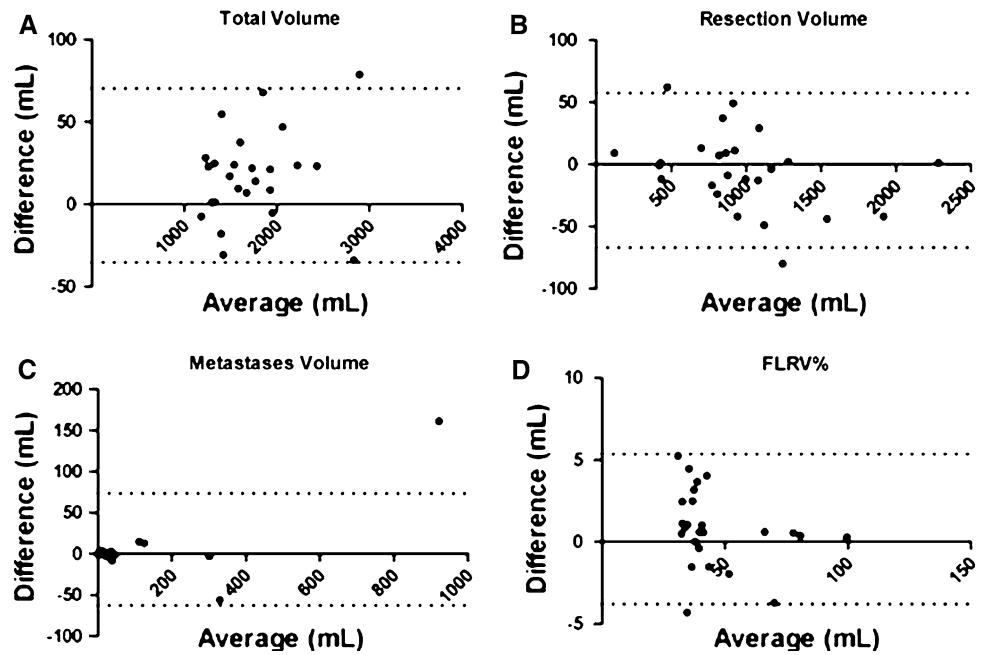

Fig. 5 **a** Mean total volume of observers 1 and 3 is plotted against the difference in total volume between observers 1 and 3. **b** Mean resection volume of observers 1 and 3 is plotted against the difference in resection volume between observers 1 and 3. **c** Mean metastases volume of observers 1 and 3 is plotted against the difference in metastases volume between observers 1 and 3. **d** Mean functional remnant liver volume as a percentage of total functional liver volume of observers 1 and 3 is plotted against the difference in functional remnant liver volume as a percentage of total functional liver volume between observers 1 and 3
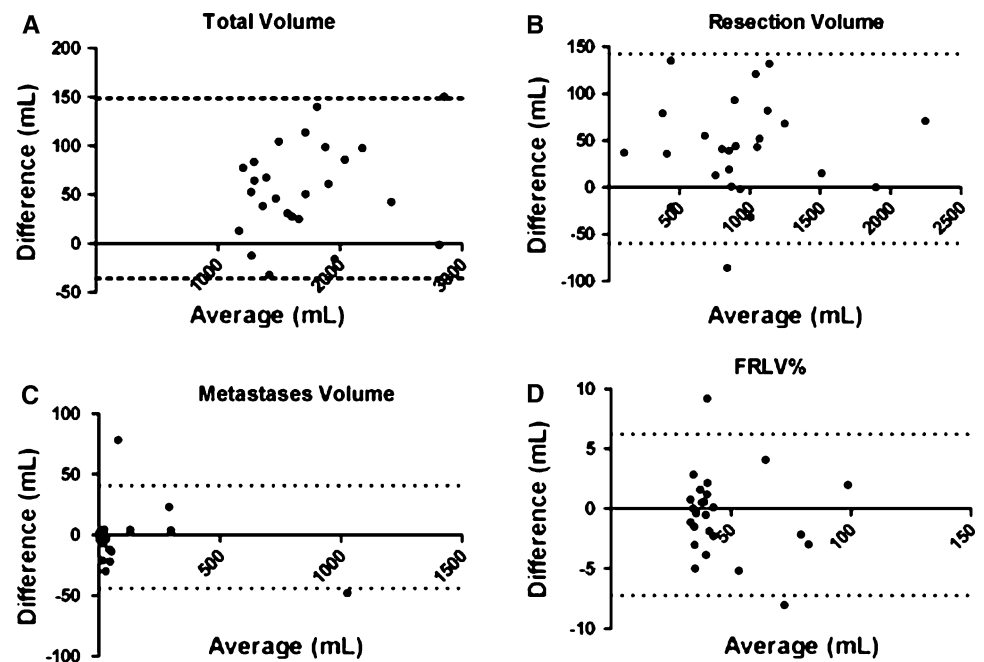
window level is changed, e.g., from abdominal to liver. This may have resulted in differences in volumetric results between the two packages as well as between subjects. Moreover, this casts some doubt as to whether iNtuition® should be considered the "gold standard" for clinical use. Terra Recon (the company that makes iNtuition®) is currently working on a solution to address this undesired phenomenon and is developing a dedicated liver tissue template. Future research will be needed to determine whether the new template is more accurate in assessing liver volume.

The mean time needed to analyze the total liver volume, tumor volume, and resection volume was 19 ± 3 min at a slice thickness of 5 mm. This is slightly faster than the time reported for ImageJ®, which is another freely downloadable open source image analysis software package [15].

This can be explained by the semiautomatic selection of the resection specimen that is possible with OsiriX®. Especially in the more caudal slices where there was a distinct difference in the Hounsfield units between liver parenchyma and the surrounding tissues, the semiautomatic contouring appeared to be very useful, fast, and precise. Additionally, it is possible to outline the liver on alternate individual slices. After outlining only half of the slices, the missing regions of interest can be generated using the "generate missing ROIs" tool in the ROI volume under the "ROI" dropdown menu. This method saves time because only small adjustments need to be made in the automatically generated regions of interest.

With OsiriX®, surgeons can perform a virtual resection to predict the future functional remnant liver volume on their own computer. This enables optimization of preoperative planning and possibly reduces the risk of postresection liver failure, especially in extended resections. Furthermore, OsiriX® has a big advantage in that it can be downloaded free of charge and it has an integrated PAC system in which the data of all examined patients are automatically stored. Nowadays, volumetric assessment of the liver is performed mainly by radiologists. At our center, the commercial image analysis software package iNtuition® is used for liver CT volumetry. This package is not readily accessible to liver surgeons and hepatologists, which sometimes makes it difficult to use when considering different scenarios in the planning of extended resections. OsiriX® combines an image archiving system and a user-friendly image analysis package. It allows one to store DICOM files of the CT scans of patients in a liver resection registry and is plug-and-play after downloading the software. However, the OsiriX® system has not yet been validated for liver volumetry.

In the past we validated ImageJ®, a software package developed by the National Institutes of Health, and found a high correlation between resection volume and actual resection weight. There are some drawbacks to ImageJ: patient DICOM files cannot be stored in a PAC system, it is not possible to semiautomatically outline the liver, and missing regions of interest cannot be generated. Although the ImageJ® system is accurate, it is our impression that it is less sophisticated than OsiriX®. A potential obstacle for liver surgeons who want to use OsiriX® is that it is only compatible with the Mac® operating system.

Although OsiriX® can be used to perform liver volumetry, it does not accurately determine preoperative liver function because volume does not always equate to function. To predict the risk of developing postresection liver failure or infection, both function and volume are important. For patients treated with preoperative chemotherapy or suffering from liver cirrhosis, a larger remnant liver volume is needed to perform a safe resection. Because an accurate liver function test is not yet available, the safety of extended resections and resections in patients pretreated with chemotherapy remains uncertain. Nevertheless, CT volumetry of extended resections will offer additional information and reduce the risk of developing postresection liver failure.

Conclusions

The high correlation between resection weight and virtual resection volume, the weight-to-volume ratios, and the acceptable low interobserver variability demonstrate that OsiriX® can be used for CT volumetry of the liver. OsiriX® accurately measures total liver volume, metastases volume, and virtual resection specimens. Using these measurements, clinicians are able to make an accurate prediction of the functional remnant liver volume. In addition, we found OsiriX® to be a very well organized and efficient CT liver volumetry software package.

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