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Liver Planning Software Accurately Predicts Postoperative Liver Volume and Measures Early Regeneration

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Abstract

Background—Postoperative or remnant liver volume (RLV) following hepatic resection is a critical predictor of perioperative outcome. This study investigates whether the accuracy of liver surgical planning software for predicting postoperative RLV and assessing early regeneration.

Study Design—Patients eligible for hepatic resection were approached for participation in the study from June 2008 to 2010. All patients underwent cross-sectional imaging (CT or MRI) prior to and early after resection. Planned remnant liver volume (pRLV) (based on the planned resection on the preoperative scan), and postoperative actual remnant liver volume (aRLV) (determined from early postoperative scan) were measured using Scout Liver software (Pathfinder Therapeutics Inc., Nashville, TN). Differences between pRLV and aRLV were analyzed controlling for timing of postoperative imaging. Measured TLV was compared against standard equations for calculating volume.

Results—Sixty-six patients were enrolled in the study from June 2008 to June 2010 at three treatment centers. Correlation was found between pRLV and aRLV ($r=0.941$, $p<0.001$), which improved when timing of postoperative imaging was considered ($r=0.953$, $p<0.001$). Relative volume deviation from pRLV to aRLV stratified cases according to timing of postoperative imaging showed evidence of measurable regeneration beginning five days after surgery with stabilization at eight days ($p < 0.01$). For patients at the upper and lower extremes of liver volumes, TLV was poorly estimated using standard equations (up to 50% in some cases).

Conclusions—Preoperative virtual planning of future liver remnant accurately predicts postoperative volume following hepatic resection. Early postoperative liver regeneration is measurable on imaging beginning at five days following surgery. Measuring TLV directly from CT scans rather than calculating based on equations accounts for extremes in TLV.

Introduction

Over the past several years, partial hepatectomy has emerged as the most effective and the only potentially curative therapy for many primary and secondary hepatic tumors (1, 2). The therapeutic advantage of resection over other treatments is now clear but has only manifested as the marked improvements in safety have been realized. Full recovery from major hepatic resection requires a healthy, well-perfused liver remnant that is capable of regenerating to its pre-resection volume. Indeed, a better appreciation of the adequacy of the future liver remnant (FLR) size and quality has represented an important safety advance in hepatic resectional surgery. Several studies have shown that the percentage of functional liver parenchyma remaining after major hepatic resection is an important predictor of postoperative hepatic dysfunction and morbidity (3-6).

In the past, liver volumetry was calculated either by using equations involving height and weight (7, 8) that fail to account for individual variability, or by manually designating liver parenchyma and tumor boundaries from cross-sectional imaging studies (3, 9), which is time consuming. In the last decade, automated and semi-automated methods of demarcating the liver from neighboring structures have been the subject of intense investigation (10), with some clinical adoption (3, 11, 12). Software tools now exist for computing hepatic volumetry and defining surgical resection margins on virtual anatomy (13, 14); however,

whether these utilities accurately predict postoperative volume is an unresolved question. Studies that correlate virtual resection volume with the volume of the resected mass do so by weighing the mass after resection and applying a conversion factor from weight to volume (1 g = 1 mL) (15) or by acquiring postoperative scans more than a week following surgery (11) after volume changes may have occurred.

This multi-center study evaluates the accuracy of surgical planning software for defining virtual cutting planes for hepatic resection. The primary aim was to correlate the volume of the virtual remnant and the volume of the actual remnant, where the postoperative volume is computed directly from postoperative imaging scans as a true measure of accuracy; the secondary aim was to assess early liver regeneration patterns in the early postoperative period.

Methods

The data reported in this study were collected during a prospective clinical trial (registration number: NCT00782886) sponsored by Pathfinder Therapeutics Inc. (Nashville, TN), supported by a grant from the Small Business Innovative Research (SBIR) fund provided by NIH/NCI titled "Evaluation of Image-Guided Liver Surgical System for Resection of Liver Cancer", and conducted at three treatment centers: University of Florida, Gainesville (UF), Memorial Sloan-Kettering Cancer Center (MSKCC), and University of Pittsburgh Medical Center (UPMC) from June 2008 through June 2010. This was a clinical trial aimed at assessing the utility and safety (phase II equivalent) of the Pathfinder intraoperative image guidance system. Institutional review board authorization was obtained from the participating institutions prior to the study. Demographic, laboratory, histopathological, operative, perioperative, and survival data were collected prospectively and analyzed retrospectively. Patients received standard contrast enhanced preoperative MRI or CT scans, as is standard practice at the participating institutions. As part of the IRB protocol, patients received a postoperative CT scan in the immediate days following surgery. Complications were graded according to the Common Toxicity Criteria (CTC) from the National Cancer Institute.

Patient Selection

Candidates for resection of malignant or benign tumors with measurable disease on preoperative imaging and surgical treatment requiring removal of at least one anatomical segment were selected for the study. Patients with cirrhosis of the liver classified as Child-Pugh score B or C, thrombocytopenia, or renal insufficiency (defined as creatinine greater than 2.5 mg/dl), were excluded from consideration. The preoperative evaluation, intraoperative management, and conduct of the operation at the 3 centers have been described previously (16-18).

Preoperative planning software

Scout Liver (Pathfinder Therapeutics, Nashville, TN) is commercially available preoperative planning software that provides 3D visualization and measurement of structures of interest in the liver using CT and MRI imaging studies. The software allows the user to manually or

semi-automatically segment the liver, intrahepatic vessels, and tumors. A sample Scout Liver after segmentation is depicted in Figure 1. Specific surgical strategies can be virtually defined by delineating resection lines and ablation paths. The software provides volumetric measurements of functional liver volume, remnant liver volume, and lesions as well as measurements of the planned resection. The software allows the user to query, choose, and pull scans directly from the patient records and communication system (PACS), requires 5-15 minutes to run and then up to 15 minutes of user interaction without the need for a radiologist.

The accuracy and repeatability of the segmentation results were independently evaluated at the Catholic University of Louvain in Belgium and were found to be more consistent but as accurate as radiologists manually designating contours (19). The algorithm for semi-automatically designating the liver contours was compared against state-of-the-art techniques from several academic institutions and scored highest overall with respect to accuracy when compared to manual techniques (10). The underlying algorithm used by the software for determining the volume of a 3D object generated from contours in CT is based on a well-established technique (20) used in most modern software packages and radiologic workstations so one would not expect software to compute more or less accurate volumes than manual techniques but rather similar volumes.

Pre- and postoperative liver volumetry measurements

The Scout Liver software calculated the patient's total liver volume (TLV) and tumor volume (TuV). The total functional liver volume (TFLV) was calculated by subtracting the TuV from the TLV: $TFLV = TLV - TuV$. Using the planning software, a virtual resection was performed according to the surgical strategy for each patient and the planned remnant liver volume (pRLV) was calculated using the software, based on the virtual resection. The relative remnant liver volume (%RLV) was expressed as: $\%RLV = pRLV/TFLV \times 100$. Immediately following surgery, the virtual plan was modified to reflect the true resection in the event that the surgeon changed the operative plan. The actual remnant liver volume (aRLV) was calculated from postoperative CT acquired within 5 days of surgery (if clinically warranted, this scan could be deferred for up to 2 weeks following surgery) and measured using the surgical planning software. The relative change from the planned to the actual remnant liver volume was calculated as $(aRLV - pRLV)/aRLV \times 100$.

The patient's body surface area (BSA) was calculated using a formula by Dubois and Dubois (21): $BSA (m^2) = weight (kg)^{0.425} \times height (cm)^{0.725}$. For comparison with the Scout Liver software, the patient's TLV was calculated using three formulas: Vauthey et al. (based on BSA): $TLV (cm^3) = -794.41 + 1,267.28 \times BSA (m^2)$ (7), Vauthey et al. (based on weight): $TLV (cm^3) = 191.80 + 18.51 \times weight (kg)$ (7), and Urata et al. (based on BSA): $TLV (cm^3) = 706.2 \times BSA (m^2) + 2.4$ (22).

Statistical analysis

Correlation and multiple linear regression analyses were conducted to examine the relationship between the postoperative volume and the timing of the postoperative scan, treatment center, resection extent, and type of preoperative imaging (CT or MRI) as

potential predictors. A regression line with aRLV as the dependent variable (y-axis) and pRLV (as predictor) was derived, and the correlation coefficient (Pearson's) was calculated. A multiple linear regression modeled the relationship between the aRLV and the pRLV and the timing of the postoperative scan. Segmented regression can help identify change points (also called breakpoint, threshold, or transition point) in the relationship between the response and some explanatory variables in a regression model (23). The change point is introduced as a parameter to the regression model along with intercepts and slopes for the subsets before and after the change point. All the coefficients are simultaneously estimated using least squares subject to the constraint that the two-lines so estimated connect at the change point. After all of the coefficients are estimated, the difference between the two slopes (before and after the change point) is compared using a maximally selected test statistic (24). The technique was used here to assess a possible threshold value in the relative difference between pRLV and aRLV (response), based on the timing of the postoperative scan and extent of resection (explanatory variables), to suggest an influence of hepatic regeneration. A mixed effects model was used to analyze differences due to treatment center and the type of preoperative imaging (CT or MRI). The 95% confidence intervals for the predicted values were calculated for each regression. An analysis of variance was used to compare TLV computed using the four methods described above with respect to treatment center. A p-value of less than 0.05 was considered to indicate significant differences. All statistical analyses were performed with a software package (SPSS, IBM Corporation).

Results

Treatment centers, demographics, operative procedures, and complications

During the two-year study period, 86 patients were approached for participation and enrolled in the study. Of the original cohort, twenty patients did not have pre and postoperative scans: 5 patients withdrew consent prior to surgery, 3 patients were deemed unresectable due to extrahepatic disease, 1 patient was admitted to ICU prior to surgery, 4 patients refused the postoperative scan, 2 patients did not receive the postoperative scan due to clinical reasons, and 5 patients logistical/equipment issues at the time of surgery, as detailed in Figure 2. Sixty-six patients had pre and postoperative scans and were therefore included in our analysis: 20 (30%) patients from UPMC, 34 (52%) from MSKCC, and 12 (18%) from UF. Patient characteristics are summarized in Table 1. Thirty-three (50%) patients were men and the median age was 54.0 years (IQR 44 to 66 years). The median body mass index (BMI) was 26.9 kg/m² (IQR 23.1 to 32.0 kg/m²).

Of the 66 enrolled patients, the majority underwent right hepatectomy (29 patients, 44%), followed by left hepatectomy (9 patients, 14%), left lateral sectionectomy (8 patients, 12%), atypical resections (7 patients, 11%), extended right hepatectomy (6 patients, 9%), right posterior sectionectomy (3 patients, 5%), segmentectomy (3 patients, 5%), and multiple wedge resections (1 patient, 2%). The extent of resection by mean relative remnant liver volume is summarized in Table 2.

All patients underwent resection with no noteworthy intraoperative events. Of the 66 patients, 23 had a total of 29 complications for a complication rate of 35%. Nineteen major complications (CTC grade 3 or more) were observed in 16 patients, for a major complication

rate of 24%. Major complications included: perihepatic seroma, pleural effusion and deep-vein thrombosis (3 patients), respiratory distress, acute respiratory failure, infection (2 patients), hemoglobin, wound infection, abdominal hemorrhage, renal failure, and fascial wound dehiscence, and sepsis with multi-organ failure. One patient died on postoperative day 22 due to heart failure.

The mean TLV calculated by the Scout software was $1816 \pm 596 \text{ cm}^3$; the mean pRLV was $1055 \pm 508 \text{ cm}^3$ while the mean aRLV was $1144 \pm 506 \text{ cm}^3$. The mean TuV measured with the Scout software was $89 \pm 200 \text{ cm}^3$. By comparison, the mean TLV calculated using the Vauthey formula based on weight (7) and based on BSA (8), and the Urata formula (22) were $1669 \pm 451 \text{ cm}^3$, $1629 \pm 419 \text{ cm}^3$, and $1331 \pm 214 \text{ cm}^3$, respectively. No significant differences were found between the liver volume as determined by the Scout software and these calculation methods; however, the formulas do not adequately capture the extremes of the study group. For example, the largest TLV measured by the software was 3526 cm^3 ; by contrast, for the same patient, the formulas predicted TLV values of 1562 cm^3 (Vauthey weight), 1589 cm^3 (Vauthey BSA), and 1322 cm^3 (Urata), severely underestimating the volume. Similarly, the smallest TLV measured by the software was 788 cm^3 ; the formulas predicted TLV was 923 cm^3 (Vauthey weight), 831 cm^3 (Vauthey BSA), and 918 cm^3 (Urata).

The timing of the postoperative scans varied based on the clinical condition of the patients in some cases and regulatory issues at one study site mandated outpatient postoperative scans. The postoperative scans were acquired at a median of 5 days following resection (IQR 3 to 6 days). With respect to timing of the postoperative scan, 52 (79%) scans were acquired within 7 days of surgery: 15 of 20 scans at UPMC (75%), 25 of 34 scans at MSKCC (74%), and 12 of 12 scans at UF (100%). Nine scans (14%) were acquired 7 to 14 days following surgery: 3 of 20 at UPMC (15%) and 6 of 34 at MSKCC (18%). The remaining scans were acquired more than 14 days after surgery: 2 of 20 at UPMC (10%) and 3 of 34 at MSKCC (9%).

Planned versus actual resection

There was a strong positive correlation between the aRLV and the pRLV ($\text{aRLV} = 0.939 \times \text{pRLV} + 157.2$, $r = 0.941$, $p < 0.001$) (Figure 3 (a)). The model accounted for approximately 89% of the variation in the aRLV. A multiple linear regression modeled the relationship between the aRLV and the pRLV and the timing of the postoperative scan. pRLV and the timing of the scan were positively correlated with aRLV ($r = 0.953$, $p < 0.01$) (Figure 3(b)). This model accounted for approximately 91% of the variation in the postoperative volume. Points above the regression line in Figure 3(b) indicate positive volume change; black points (patients with scans acquired more than 7 days following surgery) appear above and yellow points (patients with scans acquired within 1 day of surgery) lie below the line.

A mixed effects model was constructed with treatment center as a random effect and complications with CTC grade over 3, the type of preoperative imaging (CT or MRI), RLV and number of days following surgery for the postoperative scan treated as fixed effects.

Treatment center, complications, and the type of preoperative imaging did not contribute to the multiple linear regression model.

Assessment of postoperative regeneration

The timing of the postoperative scan was assessed in an attempt to identify a pattern for early postoperative liver regeneration and potentially inform early prediction of hepatic dysfunction. Computing the relative change of the liver volume from planned to actual (postoperative) and then ordering this value by timing of the scan is illustrated in Figure 4. Segmented regression (23) partitioned the relative liver volume change by the timing of the postoperative scan, with a threshold of 8 days (95% CI 5-11 days) so that the liver growth rates before and after 8 days were significantly different ($p < 0.01$). The 95th CI indicates measurable regeneration at as early as 5 days. This suggests that liver regeneration begins immediately after resection and stabilizes after 8 days (Figure 5(a)). When the extent of resection is factored into the segmented regression, the liver growth stabilizes at 6 days (95% CI 4-9 days, $p < 0.01$ for comparing growth rates before and after 6 days) for major resections (four or more segments resected) (Figure 5(b)). The relative liver volume change in the first 6 days is significantly higher for major resections as compared to minor ones ($p < 0.01$). No significant differences were found with respect to complications so hepatic dysfunction could not be assessed.

Discussion

Accurate preoperative assessment and planning are critically important for hepatic resectional surgery, not only to ensure appropriate management of the neoplastic disease, but equally important, to ensure the presence of an adequate liver remnant. The importance of the latter for major hepatic resections is clear, with several reports showing the close association between FLR volume and perioperative outcome. Cross-sectional imaging studies remain the predominant modality used in this process, although 3D planning software is being used with greater frequency.

The principal finding of the present study is that postoperative liver volume can be accurately predicted using preoperative planning software; there was a very strong positive correlation between the pRLV and the aRLV measured from postoperative scans ($r = 0.941$, $p < 0.001$). Other studies that assess the accuracy of virtual planning tools do so by comparing the volumes measured by the software with manual measurements (19, 25), weighing the resected mass and applying a conversion factor from weight to volume (15, 26), or comparison to postoperative images acquired more than a week after surgery (11, 27). The unique aspect of the present work is the very early time after surgery when the postoperative scans were acquired (median = 5 days, IQR = 3 to 6 days). Accuracy was assessed by directly comparing the planned and true volumes segmented using the same software with images from the same imaging protocol to avoid potential errors in RLV comparisons between two different modalities. One limitation of the study is that the planned future liver remnant may vary from the exact transection plane carried out in surgery. The planned resection plane was revisited after the procedure in this study to account for changes in resection strategy, but given that the liver volume in the

postoperative scans was highly correlated with the planned volume, this effect was likely minimized.

The results also underscore potential inaccuracies in the determination of liver volumes using calculation-based methods, which were inaccurate at the extremes of the size range. These calculations are based on studies of the correlation between TLV measured from CT scans related to BSA and weight (7, 22, 28). The formulae were derived from regression lines fit to these data. Inaccuracies are due to the fact that not all individuals fall on this line; some have higher or lower than average liver volumes. This is evidenced in the original studies where outliers are visible on the regression plots. The calculation-based approaches represent an easy method to predict standardized liver volumes but do not necessarily capture volumes at the extremes of the size range.

Using the planning software for resection planning and FLR volume calculation has several advantages over the conventional technique. The software derives measurements from cross-sectional 3D imaging from CT or MRI rather than from 2D images, which are less accurate due to missing information in one dimension for volumetric evaluation. For example, Pomfret *et al.* showed that CTA over-estimated liver graft weight by nearly 10% (29). Modern radiological workstations also derive measurements from 3D images; the accuracy of the Scout software is in line with such systems (19). The primary advantages of the software are with respect to the automation and ease of use. In our experience, complete processing from pulling the images from institutional storage to generating 3D models of the liver, tumors, venous structures, and resection boundaries requires 30 minutes (with some inactive time), which is an improvement over other software that can take up to two hours (13). The Scout software requires limited technical and medical knowledge (basic medical knowledge is required for designating structures for initialization of segmentation algorithms and determination of tumors); it is useful to have a clinician (radiologist or surgeon) verify virtual planning performed by an operator. While not a replacement for radiological expertise, the software represents a mechanism by which image volumes can be pulled from PACS and assessed on any institutional workstation without a radiologist. One of the benefits of planning software in general (be it Scout or another software package) is the ability to visualize in 3D the precise structure of the tumor location relative to the surrounding major vascular and biliary structures and to determine whether complete extirpation of the disease is possible while maintaining an adequate liver remnant volume with intact vascular inflow and outflow and biliary drainage (13). Without planning software, however, it can be difficult to obtain this information in a manner that optimally facilitates the resection since the surgeon must undertake the complex mental task of reconstructing 3D image volumes from 2D slices. Planning software is an effective way to measure hepatic volumetry and may be helpful in assessing pre and post embolization changes and long-term postoperative liver generation: potential topics for further research.

Hepatic regeneration is a critical process after resection but remains incompletely defined. For nearly 30 years, CT volumetry has been used to study liver regeneration after major hepatic resection for liver donation and resection of malignant tumors (30-32). The rate of hepatic regeneration in normal livers is thought to start with a rapid increase in the first two weeks after surgery, followed by a decrease (possibly due to reduction in edema), and a slow

and steady increase (32, 33), and is influenced by liver function (30, 33, 34) and obesity (35). Whether the extent of resection correlates with regeneration rate is debatable (27, 33). Studies of early liver regeneration (1 week after surgery), and particularly, analyses of regeneration immediately after surgery, are rare (29, 32, 34). In the present study, the mean remnant was 58% of the original volume at the time of surgery and 64% of the original volume by the first postoperative scan, which indicates earlier regeneration than the 28 to 64% volume regeneration within two weeks of surgery reported in other studies.

While prior studies have demonstrated liver regeneration in the week after resection, the current study quantifies this further by providing convincing evidence that measurable changes in remnant liver volume, using contemporary imaging techniques, begin approximately five days following surgery ($p < 0.01$) and begin at six days in major resections ($p < 0.01$). The timing of the postoperative scan in the study cohort may influence this cutoff value (median of five days, IQR 3 to 6 days). However, since early postoperative scans are not the standard of care, scans from a more appropriate time frame are unavailable for study. This early phase of liver regeneration accounts for the large majority of the size increase and would therefore appear the most critical. Whether assessment of the early regenerative process can predict perioperative outcome is unknown. In the present study, there was no clear demonstration that perioperative morbidity adversely impacted regeneration in the early stages: there were no cases of liver failure in this patient cohort and a relatively low complication rate. This may be due to patient selection in the context of the clinical trial; patients were generally healthy with lower risk resections but a definitive conclusion in this regard will require a larger, more comprehensive analysis.

Conclusion

This study demonstrates that preoperative virtual planning of the future liver remnant accurately predicts postoperative volume following hepatic resection. Liver volume calculations using the Scout liver software represent direct volume measures, and therefore account more fully for patients at the extremes of liver size ranges. Early postoperative liver regeneration is observable and measureable on imaging beginning five days following surgery.

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References

1. Rosen CB. Management of hepatic metastases. *Cancer Control*. 1998; 5:30–31. [PubMed: 10762479]
2. Sardi A, Akbarov A, Conaway G. Management of primary and metastatic tumors to the liver. *Oncology*. 1996; 10:911–925. discussion 926, 929-930. [PubMed: 8823803]
3. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg*. 2003; 7:325–330. [PubMed: 12654556]

4. Schindl MJ, Redhead DN, Fearon KCH, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. *Gut*. 2005; 54:289–296. [PubMed: 15647196]
5. Kishi Y, Abdalla EK, Chun YS, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg*. 2009; 250:540–548. [PubMed: 19730239]
6. Shirabe K, Shimada M, Gion T, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg*. 1999; 188:304–309. [PubMed: 10065820]
7. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. *Liver Transplant*. 2002; 8:233–240.
8. Andreou A, Kopetz S, Maru DM, et al. Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases. *Ann Surg*. 2012; 256:642–650. [PubMed: 22968062]
9. Heymsfield SB, Fulenwider T, Nordlinger B, et al. Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. *Ann Int Med*. 1979; 90:185–187. [PubMed: 443650]
10. Heimann T, van Ginneken B, Styner MA, et al. Comparison and evaluation of methods for liver segmentation from CT datasets. *IEEE Trans Med Imaging*. 2009; 28:1251–1265. [PubMed: 19211338]
11. Karlo C, Reiner CS, Stolzmann P, et al. CT- and MRI-based volumetry of resected liver specimen: Comparison to intraoperative volume and weight measurements and calculation of conversion factors. *Eu J Radiol*. 2010; 75:e107–e111.
12. Nakayama Y, Li Q, Katsuragawa S, et al. Automated hepatic volumetry for living related liver transplantation at multisection CT. *Radiology*. 2006; 240:743–748. [PubMed: 16857979]
13. Mise Y, Tani K, Aoki T, et al. Virtual liver resection: computer-assisted operation planning using a three-dimensional liver representation. *J Hepatobiliary Pancreat Sci*. 2012:1–8.
14. Simpson, AL.; Dumpuri, P.; Jarnagin, WR.; Miga, MI. Model-Assisted Image-Guided Liver Surgery Using Sparse Intraoperative Data. In: Payan, Y., editor. *Soft Tissue Biomechanical Modeling for Computer Assisted Surgery*. Studies in Mechanobiology, Tissue Engineering and Biomaterials. Vol. 11. Springer Berlin Heidelberg; 2012. p. 7-40.
15. Ariizumi, Si; Takahashi, Y.; Kotera, Y., et al. Novel virtual hepatectomy is useful for evaluation of the portal territory for anatomical sectionectomy, segmentectomy, and hemihepatectomy. *J Hepatobiliary Pancreat Sci*. 2012:1–7.
16. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg*. 2002; 236:397–406. discussion -407. [PubMed: 12368667]
17. Hemming AW, Reed AI, Langham MR, et al. Hepatic vein reconstruction for resection of hepatic tumors. *Ann Surg*. 2002; 235:850–858. [PubMed: 12035042]
18. Balaa FK, Gamblin TC, Tsung A, et al. Right hepatic lobectomy using the staple technique in 101 patients. *J Gastrointest Surg*. 2008; 12:338–343. [PubMed: 17701266]
19. Hermoye L, Laamari-Azjal I, Cao Z, et al. Liver segmentation in living liver transplant donors: comparison of semiautomatic and manual methods. *Radiology*. 2005; 234:171–178. [PubMed: 15564393]
20. Alyassin AM, Lancaster JL, Hunter Downs I, Fox PT. Evaluation of new algorithms for the interactive measurement of surface area and volume. *Medical Physics*. 1994; 21:741–752. [PubMed: 7935209]
21. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Nutrition*. 1989; 5:303–311. [PubMed: 2520314]
22. Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. *Hepatology*. 1995; 21:1317–1321. [PubMed: 7737637]
23. Muggeo VM. Estimating regression models with unknown break-points. *Statistics Med*. 2003; 22:3055–3071.

24. Davies RB. Hypothesis testing when a nuisance parameter is present only under the alternatives. *Biometrika*. 1987; 74:33–43.
25. Lang H, Radtke A, Hindennach M, et al. Impact of virtual tumor resection and computer-assisted risk analysis on operation planning and intraoperative strategy in major hepatic resection. *Arch Surg*. 2005; 140:629–638. discussion 638. [PubMed: 16027326]
26. Saito S, Yamanaka J, Miura K, et al. A novel 3D hepatectomy simulation based on liver circulation: application to liver resection and transplantation. *Hepatology*. 2005; 41:1297–1304. [PubMed: 15846773]
27. Kele PG, de Boer M, van der Jagt EJ, et al. Early hepatic regeneration index and completeness of regeneration at 6 months after partial hepatectomy. *Br J Surg*. 2012; 99:1113–1119. [PubMed: 22696005]
28. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery*. 2000; 127:512–519. [PubMed: 10819059]
29. Pomfret EA, Pomposelli JJ, Gordon FD, et al. Liver regeneration and surgical outcome in donors of right-lobe liver grafts. *Transplantation*. 2003; 76:5–10. [PubMed: 12865779]
30. Chen MF, Hwang TL, Hung CF. Human liver regeneration after major hepatectomy. A study of liver volume by computed tomography. *Ann Surg*. 1991; 213:227–229. [PubMed: 1998403]
31. Nagino M, Ando M, Kamiya J, et al. Liver regeneration after major hepatectomy for biliary cancer. *Br J Surg*. 2001; 88:1084–1091. [PubMed: 11488794]
32. Zappa M, Dondero F, Sibert A, et al. Liver regeneration at day 7 after right hepatectomy: global and segmental volumetric analysis by using CT. *Radiology*. 2009; 252:426–432. [PubMed: 19703882]
33. Yamanaka N, Okamoto E, Kawamura E, et al. Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on the basis of computed tomography and liver function. *Hepatology*. 1993; 18:79–85. [PubMed: 8392029]
34. Ju MK, Choi GH, Park JS, et al. Difference of regeneration potential between healthy and diseased liver. *Transplant Proc*. 2012; 44:338–340. [PubMed: 22410010]
35. Lock JF, Malinowski M, Seehofer D, et al. Function and volume recovery after partial hepatectomy: influence of preoperative liver function, residual liver volume, and obesity. *Langenbeck's archives of surgery / Deutsche Gesellschaft für Chirurgie*. 2012; 397:1297–1304.
36. Bowman, AW.; Azzalini, A. *Applied Smoothing Techniques for Data Analysis: The Kernel Approach with S-Plus Illustrations*. New York: Oxford University Press Inc.; 1997.

Abbreviations and Acronyms

aRLV	actual remnant liver volume
BMI	body mass index
BSA	body surface area
CT	computed tomography
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
pRLV	planned remnant liver volume
RLV	remnant liver volume
%RLV	percentage remnant liver volume
TFLV	total functional liver volume

TLV	total liver volume
TuV	tumor volume
UF	University of Florida
UPMC	University of Pittsburgh Medical Center

Figure 1.

Sample data from Scout Liver planning software: (left) CT image with boundaries of organ indicated by green contour and (right) 3D model of organ with hepatic (red) and portal (blue) venous systems, tumor (brown), and resection plane.

Figure 2.
Trial profile.

Figure 3.

(A) Scatterplot of the regression analysis with the planned RLV (virtual resection) and the actual RLV (postoperative CT volume) with the 95% confidence interval. There is good correlation between the planned RLV and postoperative volume ($aRLV = 0.939 \cdot pRLV + 157.2$, $p < 0.001$). The p value is testing whether the slope of the line is zero. (B) Scatterplot colored by the timing of the postoperative CT. Note that the data points of earlier scans fall below the line and later scans above the line.

Figure 4.

Plot showing the relative percent change from the planned to the actual RLV, in increasing order by number of days following surgery in which postoperative CT was acquired beginning with one day (far left) to over 5 days (far right, in red). It appears that as soon as five days after surgery, the liver shows some measurable volume increases.

Figure 5.

Relative change from the planned to the actual resection plotted against the timing for the postoperative scan. (A) The black dots represent the data, the black line is the mean relative change for each day, and the red line represents the smoothed mean (36). (B) The red dots represent major resections (more than 4 segments resected) and the black dots the minor resections (less than 3 segments resected). The lines represent the smoothed means for each group. Relative change = $(aRLV - pRLV)/aRLV \times 100$.

Table 1
Clinicopathological Factors of Patients Who Underwent Resection after Preoperative Planning (n = 66)

Clinicopathological Factor	All patients
Treatment center, n (%)	
UPMC	20 (30)
MSKCC	34 (52)
UF	12 (18)
Age, y, median (IQR)	54 (44-66)
Gender, n (%)	
Male	33 (50)
Female	33 (50)
Weight, kg, median (IQR)	77 (61-92)
Height, cm, median (IQR)	169 (160-176)
Body mass index, kg/m ² , median, (IQR)	26.9 (23.1-32.0)
Body surface area, m ² , median, (IQR)	1.9 (1.7-2.1)
Scout TLV, cm ³ (mean ± SD)	1816 ± 596
Planned RLV, cm ³ (mean ± SD)	1055 ± 508
Actual RLV, cm ³ (mean ± SD)	1144 ± 506
%RLV (mean ± SD)	61.1 ± 21.5
Tumor volume, cm ³ (mean ± SD)	89 ± 200
Tumor(s), median (IQR)	1 (1-3)
Postoperative CT timing, days, median (IQR)	5 (3-6)
Mortality, n (%)	1 (2)
Complications, n (%)	23 (35)
Margin status, n (%)	
Negative	59 (89)
Positive	7 (11)
Diagnosis, n (%)	
Metastatic CRC	36(55)
Hepatocellular cancer	8 (12)
Cholangiocarcinoma	8 (12)
Benign	7 (11)
Other*	7 (11)

* Gastrointestinal stromal tumor, anal cancer, liver angiosarcoma, breast cancer, hemangiopericytoma, gallbladder cancer, and germ cell carcinoma.

UPMC, University of Pittsburgh Medical Center; MSKCC, Memorial Sloan Kettering Cancer Center; UF, University of Florida; TLV, total liver volume; RLV, remnant liver volume; CRC, colorectal cancer; pRLV, predicted RLV; TFLV, total functional liver volume; %RLV, pRLV/TFLV × 100.

Table 2
Extent of Resection Therapy by Mean Relative Remnant Liver Volume (%RLV) for 66 Patients

Type of Resection	n	%RLV (Mean $\pm$ SD)
Extended right hepatectomy	6	39.7 $\pm$ 3.5
Right hepatectomy	29	43.2 $\pm$ 7.2
Right posterior sectorectomy	3	73.9 $\pm$ 2.4
Left hepatectomy	9	75.2 $\pm$ 8.4
Left lateral segmentectomy	8	81.8 $\pm$ 9.9
Segmentectomy	3	87.8 $\pm$ 15.0
Atypical resections*	7	89.7 $\pm$ 3.8
Multiple wedge resections†	1	95.2 $\pm$ 0.0

* One segment resected.

† Two segments resected.

RLV, remnant liver volume; pRLV, predicted RLV; TFLV, total functional liver volume; %RLV = pRLV/TFLV $\times$ 100.