Remnant Growth Rate after Portal Vein Embolization Is a Good Early Predictor of Post-Hepatectomy Liver Failure

Universe Leung, MBChB, FRACS, Amber L Simpson, PhD, Raphael LC Araujo, MD, Mithat Gönen, PhD, Conor McAuliffe, BA, Michael I Miga, PhD, E Patricia Parada, BS, Peter J Allen, MD, FACS, Michael I D'Angelica, MD, FACS, T Peter Kingham, MD, FACS, Ronald P DeMatteo, MD, FACS, Yuman Fong, MD, FACS, William R Jarnagin, MD, FACS

BACKGROUND: After portal vein embolization (PVE), the future liver remnant (FLR) hypertrophies for several weeks. An early marker that predicts a low risk of post-hepatectomy liver failure can reduce the delay to surgery.

STUDY DESIGN: Liver volumes of 153 patients who underwent a major hepatectomy (>3 segments) after PVE for primary or secondary liver malignancy between September 1999 and November 2012 were retrospectively evaluated with computerized volumetry. Pre- and post-PVE FLR volume and functional liver volume were measured. Degree of hypertrophy (DH = post-FLR/post-functional liver volume − pre-FLR/pre-functional liver volume) and growth rate (GR = DH/weeks since PVE) were calculated. Postoperative complications and liver failure were correlated with DH, measured GR, and estimated GR derived from a formula based on body surface area.

RESULTS: Eligible patients underwent 93 right hepatectomies, 51 extended right hepatectomies, 4 left hepatectomies, and 5 extended left hepatectomies. Major complications occurred in 44 patients (28.7%) and liver failure in 6 patients (3.9%). Nonparametric regression showed that post-embolization FLR percent correlated poorly with liver failure. Receiver operating characteristic curves showed that DH and GR were good predictors of liver failure (area under the curve [AUC] = 0.80; p = 0.011 and AUC = 0.79; p = 0.015) and modest predictors of major complications (AUC = 0.66; p = 0.002 and AUC = 0.61; p = 0.032). No patient with GR >2.66% per week had liver failure develop. The predictive value of measured GR was superior to estimated GR for liver failure (AUC = 0.79 vs 0.58; p = 0.046).

CONCLUSIONS: Both DH and GR after PVE are strong predictors of post-hepatectomy liver failure. Growth rate might be a better guide for the optimum timing of liver resection than static volumetric measurements. Measured volumetrics correlated with outcomes better than estimated volumetrics. (J Am Coll Surg 2014;219:620−630. © 2014 by the American College of Surgeons)

In patients undergoing liver resection, the optimal future liver remnant (FLR) volume required for safe recovery is uncertain. For patients with normal liver parenchyma, 20% to 40% of the total liver volume has been suggested as the minimum,[1-7] and patients with underlying hepatic parenchymal disease (ie, steatosis, chemotherapy-associated liver injury, or cirrhosis) are believed to require larger percentage volumes.[8,9] Portal vein embolization

Disclosure Information: Dr Miga receives royalties and owns stock in Pathfinder Therapeutics, Inc.; Ms Parada is an employee of Pathfinder Therapeutics, Inc.; and Dr Kingham has received support for travel to meetings for this study from Pathfinder Therapeutics, Inc. All other authors have nothing to declare.

Support: This study was supported by the following NIH/National Cancer Institute awards: R01 CA162477 and P30 CA008748 (Cancer Center Support Grant).

Received February 24, 2014; Revised April 6, 2014; Accepted April 7, 2014.

From the Hepatopancreatobiliary Service, Department of Surgery (Leung, Simpson, Araujo, McAuliffe, Allen, D'Angelica, Kingham, DeMatteo, Fong, Jarnagin) and Department of Epidemiology and Biostatistics (Gönen), Memorial Sloan Kettering Cancer Center, New York, NY, Department of Biomedical Engineering, Vanderbilt University (Simpson, Miga), and Pathfinder Therapeutics Inc. (Parada), Nashville, TN.

Correspondence address: William R Jarnagin, MD, FACS, Hepatopancreatobiliary Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, C-891, New York, NY 10065. email: jarnagiw@mskcc.org

http://dx.doi.org/10.1016/j.jamcollsurg.2014.04.022
ISSN 1072-7515/14

Abbreviations and Acronyms
AUC = area under the curve
eGR = estimated growth rate
FLR = future liver remnant
FLV = functional liver volume
IQR = interquartile range
PVE = portal vein embolization
ROC = receiver operating characteristic
sFLR = standardized future liver remnant

(PVE) has become an important means to increase the FLR volume before major hepatectomy and thereby reduce postoperative liver failure. After an ill-defined period of time, usually 4 to 6 weeks, repeat imaging is used to determine if the minimum volume has been achieved and to decide if it is safe to proceed to surgery. However, the predictive value of these static measures is variable and not well studied in the post-PVE setting.

Typically, hepatectomy is performed several weeks after PVE to allow for adequate hypertrophy of the FLR. Correa and colleagues[10] showed that liver hypertrophy after PVE is more gradual than after hepatectomy, with only 25% of the eventual volume gained after 1 month. Continued growth has been observed for up to 1 year. A reliable early marker of adequate response after PVE is desirable, as it would not only predict successful perioperative outcomes, but would also support reduction of the delay between PVE and subsequent resection. Conversely, patients predicted to do poorly, even if their eventual post-hepatectomy volume gain appears sufficient, would be approached more cautiously or alternative nonresectional treatment would be sought. One such potential marker is the growth rate, which can be measured relatively early after PVE, before full hypertrophy has occurred. Shindoh and colleagues[11] recently reported the promising predictive value of growth rate for patients with colorectal liver metastases undergoing right hepatectomy.

The size of the FLR is typically expressed as a percentage of the functional liver volume (FLV). There is controversy about the optimum method of measuring FLR, which is traditionally done using computerized volumetry from CT or MRI,[5] although some advocate estimation of the FLV using a formula based on body surface area.[12] The ratio of the measured FLR to the estimated FLV has been termed *standardized FLR*, from which a rate of growth can be derived.

The current study examines the FLR growth rate in a broad population of patients submitted to PVE and correlates it to post-hepatectomy liver failure and overall morbidity. We also compared the measured growth rates and estimated growth rates (eGR) and assessed the ability of each to predict perioperative outcomes.

METHODS

The Institutional Review Board at Memorial Sloan Kettering Cancer Center granted a waiver of consent for this retrospective study. Two hundred and fourteen patients who underwent preoperative PVE followed by major hepatectomy (≥3 Couinaud segments) for malignant liver disease (primary and secondary) between September 1999 and November 2012 were identified from a prospectively maintained database. Patients were eligible if a CT or MRI scan was performed both before PVE and after PVE, but before hepatectomy. Thirty-three patients were excluded from the study because one or more required scans were missing, imaging coverage of the liver was incomplete, imaging quality was inadequate, or if one or more scans were from an external imaging source. An additional 28 patients were excluded if surgery was delayed for more than 3 months for any reason. A total of 153 patients were included in the analysis. Demographic, clinical, pathologic, and follow-up data were obtained from the database.

Embolization technique

The technique of PVE at our institution has been described previously.[13] In summary, an ipsilateral portal vein puncture was used to avoid injuring the FLR. Embolization was performed using polyvinyl alcohol particles. For right PVE, which represented the large majority of patients, the main right portal vein was embolized. When an extended right hepatectomy was planned, segment 4 portal inflow was not embolized in all except 4 patients, with the rationale being to avoid inadvertent reflux of embolic material into the remainder of the left portal system. Likewise, for a planned extended left hemihepatectomy, only the left portal vein was embolized.

Image processing

The pre- and post-PVE CT or MRI scans were processed using PC-based software (Scout Liver; Pathfinder Therapeutics). The liver was outlined on an axial scan in a semiautomated fashion; manual adjustment was usually needed to ensure that extrahepatic structures, such as the inferior vena cava, the base of the heart, and the abdominal wall, were excluded. Once designation of the liver extent was complete, a three-dimensional model of the organ was generated. The software computed the volume of the liver using a well-established technique.[14] The volume of tumors was calculated similarly. The 3-dimensional model was then manually divided into the embolized (resected) and nonembolized (remnant) sides along the principal plane of the liver defined by the middle hepatic vein and the gallbladder fossa.

The following volumetric data were obtained: total liver volume, total tumor volume, functional liver volume (FLV = total liver volume − total tumor volume),

functional volume of embolized lobe, functional volume of nonembolized lobe (FLR). Data were obtained for both the pre-PVE and post-PVE scans. The FLR was based on the pattern of embolization, which in patients undergoing a right hepatectomy, closely approximated the actual FLR. The degree of hypertrophic response, which measured the difference between the percentage volumes before and after PVE, was defined as degree of hypertrophy (%) = (post-FLR × 100/post-FLV) − (pre-FLR × 100/pre-FLV). The growth rate was defined as the degree of hypertrophy per week after PVE.

We measured FLR using computerized volumetry. An additional analysis was performed based on estimated liver volume calculated from patient body surface area, using a technique that has been described previously.[12] From the estimated liver volume, an estimated future liver remnant percentage, estimated degree of hypertrophy, and eGR were derived.

Definitions

Complications were prospectively recorded and graded from 0 to 5 using a previously reported and validated serious adverse events classification system developed at our institution, with 0 indicating no complication, and 5 indicating death.[15] In this study, a major complication was defined as grade 3 or higher. Liver failure was defined using the "50-50 criteria" described previously by Balzan and colleagues[16] as a serum bilirubin >50 μmol/L and prothrombin time <50% on postoperative day 5.

Comparisons

The volumetric parameters of patients who did and did not have liver failure develop were compared, as were the parameters of patients who did and did not have major complications develop. The predictive strengths of the post-PVE remnant volume, degree of hypertrophy, growth rate, and eGR with regard to outcomes were also compared.

Statistical analysis

Mann-Whitney U test was performed on medians for covariates with continuous outcomes, and Fisher exact test was performed on covariates with dichotomous outcomes. These were analyzed using Prism (version 6.0, GraphPad). A p value of <0.05 was considered statistically significant. The associations between various versions of growth rate and the clinical outcomes (major complication or liver failure) were modeled using nonparametric regression with a local likelihood smoother.[17] Receiver operating characteristic curves (ROC) and the area under the curve (AUC) were used to evaluate the ability of growth rates to discriminate between patients who had clinical events (major complication or liver failure) and those who did not.[18] An AUC >0.5 is considered discriminative and a p value of <0.05 was considered statistically significant. The performance of the ROC for measured growth rate was compared with that for eGR using a permutation test.[19]

RESULTS

Liver failure

Table 1 summarizes the baseline and treatment characteristics for all patients and for patients with and without liver failure. The majority of patients (89.5%) had colorectal metastases. One hundred and twenty-six patients (82.3%) had received systemic chemotherapy, including 37.9% treated with oxaliplatin and 44.4% with irinotecan. Thirty-five patients (22.9%) had been treated with hepatic arterial infusion pump chemotherapy. The most common operation was right hepatectomy (60.8%), followed by extended right hepatectomy (33.3%), extended left hepatectomy (3.3%), and left hepatectomy (2.6%). Baseline characteristics were comparable between the 2 groups, except a higher proportion of patients with liver failure had hepatocellular carcinoma. Volumetric data are also presented. After a median of 27 days after PVE, a median FLR/FLV of 45.3% (interquartile range [IQR] 39.7% to 50.4%) and a median degree of hypertrophy of 9.6% (IQR 6.8% to 12.4%) were achieved. The median growth rate was 2.48% per week (IQR 1.66% to 3.44% per week). Figure 1 shows the trajectory of FLR growth after PVE. The post-PVE FLR/FLV percent was not significantly different between the 2 groups ($p = 0.07$). Patients in whom liver failure did not develop had higher degrees of hypertrophy and growth rate than patients who did have liver failure, and the difference was statistically significant.

Complications

One hundred and thirty-eight complications occurred in 87 patients (56.8%). The median grade of complication was 2. The most common complications, in descending order of incidence, were intra-abdominal collections or abscesses (n = 39), wound infections (n = 23), venous thromboembolism (n = 12), and paralytic ileus (n = 8). Major complications (grade ≥3) are summarized in Table 2. Fifty-three major complications (34.6%) occurred in 44 patients (28.7%). The majority were related to intra-abdominal collections, including abscesses and biloma. Six patients had liver failure develop (3.9%). There were 5 deaths, 3 of which were a consequence of liver failure. Two patients died of cardiac complications.

Table 3 summarizes the baseline and treatment characteristics and volumetric data for patients with and without major complications. Baseline characteristics were comparable, except that patients who had major

Table 1. Baseline and Treatment Characteristics for Patients With and Without Liver Failure

Characteristics	All patients	No liver failure	Liver failure	p Value
Total patients, n	153	147	6	
Age, y, median (IQR)	57 (50–65)	55 (50–65)	62 (57–68)	0.18
Males, n (%)	95 (62.1)	90 (61.2)	5 (83.3)	0.41
BMI, kg/m^2, median (IQR)	27.3 (24.7–30.5)	27.5 (24.7–30.7)	25.7 (24.9–27.1)	0.28
Histology, n (%)				
Colorectal metastases	137 (89.5)	133 (90.5)	4 (67)	0.12
Non–colorectal metastases	5 (3.3)	5 (3.4)	0	1.00
Hepatocellular carcinoma	6 (3.9)	4 (2.7)	2 (33)	0.02
Primary biliary carcinoma	5 (3.3)	5 (3.4)	0	1.00
Comorbidities, n (%)				
Diabetes	9 (5.9)	9 (6.1)	0	1.00
Moderate or severe steatosis	14 (9.2)	14 (9.5)	0	1.00
Cirrhosis	2 (1.3)	1 (0.7)	1 (17)	0.08
Chemotherapy within 6 mo, n (%)				
Any	126 (82.3)	122 (83.0)	4 (67)	0.29
5-FU	120 (78.4)	116 (78.9)	4 (67)	0.61
Oxaliplatin	58 (37.9)	57 (38.8)	1 (17)	0.41
Irinotecan	68 (44.4)	65 (44.2)	3 (50)	1.00
Bevacizumab	28 (18.3)	27 (18.4)	1 (17)	1.00
Hepatic arterial infusion pump FUDR	35 (22.9)	32 (21.8)	3 (50)	0.13
Operation, n (%)				
Right hemihepatectomy	93 (60.8)	90 (61.2)	3 (50)	0.68
Extended right hemihepatectomy	51 (33.3)	48 (32.7)	3 (50)	0.40
Left hemihepatectomy	4 (2.6)	4 (2.7)	0	1.00
Extended left hemihepatectomy	5 (3.3)	5 (3.4)	0	1.00
Days from PVE to post-PVE scan, median (IQR)	27 (20–33)	27 (20–33)	25 (21–27)	0.41
Volumetrics, mL, median (IQR)				
Pre-PVE FLV	1,636 (1,437–1,885)	1,640 (1,437–1,902)	1,514 (1,438–1,728)	0.42
Pre-PVE FLR	560 (473–678)	566 (473–679)	528 (513–578)	0.50
Pre-PVE FLR/FLV %	35.3 (29.8–40.1)	35.3 (29.9–39.8)	37.2 (28.9–43.0)	0.87
Post-PVE FLV	1,626 (1,443–1,846)	1,631 (1,438–1,848)	1,604 (1,524–1,701)	0.90
Post-PVE FLR	725 (628–884)	732 (622–887)	687 (646–713)	0.18
Post-PVE FLR/FLV %	45.3 (39.7–50.4)	45.6 (39.8–50.6)	40.7 (38.7–42.0)	0.07
Degree of hypertrophy, %	9.64 (6.75–12.36)	9.76 (6.92–12.5)	3.88 (−0.07 to 7.84)	0.01
Growth rate, % per week	2.48 (1.66–3.44)	2.55 (1.74–3.45)	1.23 (0.01–2.11)	0.01
eFLV	1,708 (1,485–1,946)	1,708 (1,486–1,952)	1,678 (1,463–1,760)	0.54
eGR, % per week	2.25 (1.41–3.28)	2.25 (1.44–3.26)	1.71 (0.85–3.19)	0.49

eFLV, estimated functional liver volume based on body surface area[12]; eGR, estimated growth rate; FLR, future liver remnant; FLV, functional liver volume; FUDR, floxuridine; IQR, interquartile range; PVE, portal vein embolization.

complications were more likely to have been treated with oxaliplatin ($p = 0.01$) than with irinotecan ($p = 0.02$). Patients who did not have major complications had a higher degree of hypertrophy and growth rate than patients who had major complications, and the difference was statistically significant.

Predictors of outcomes

Nonparametric regression was performed to demonstrate the relationship between the probability of liver failure or major complications and volumetric parameters. A steeper slope indicates that a predictor has a stronger association with the outcomes of interest. Figures 2A and B show that the post-embolization remnant percentage correlated poorly with liver failure and only moderately with major complications.

Figure 3A shows the correlation between growth rate and liver failure. In contrast to Figure 2A, there is a steep curve at lower growth rates, which flattens around a mean of 2.65% per week. These results suggest that growth rate

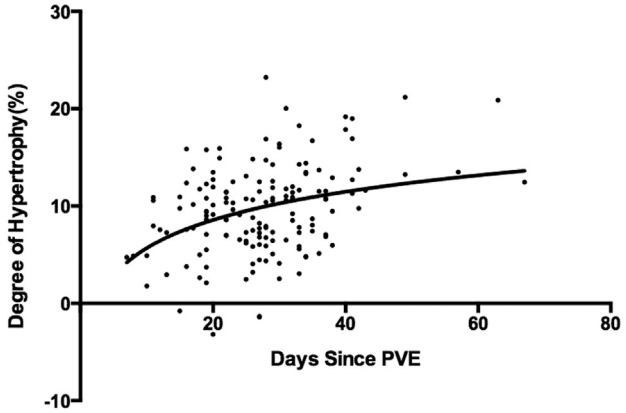

Figure 1. Growth of liver remnant over time. PVE, portal vein embolization.

was highly predictive of liver failure at low rates but not at high rates. In addition, there were no patients with liver failure where growth rate was >2.66% per week. A similar regression for major complications showed a shallower slope, indicating a weaker correlation between growth rate and complications. However, major complications were predicted through the full range of growth rates (Fig. 3B).

Figures 4A and B show the relationship between outcomes and eGR based on formula-derived estimated liver volume. The correlations were weaker than those in Figure 3.

Receiver operating characteristic curves were used to quantify the predictive strength of growth parameters. Area under the curve was calculated for each parameter with its associated p value. An AUC of 0.5 indicates that the parameter has no discriminative power for the outcomes measured, and an AUC of 1.0 indicates a perfect predictor. A summary of AUCs for the different parameters is presented in Table 4.

Table 2. Major Complications

Major complications	n	%
Total	53	34.6
Liver failure	6	3.9
Fluid collection/abscess/biloma	28	18.3
Other liver specific complication	2	1.3
Hemorrhage	3	2.0
Gastrointestinal	3	2.0
Cardiac	2	1.3
Respiratory	3	2.0
Wound	3	2.0
Nonsurgical site infection	3	2.0
Venous thromboembolism	2	1.3
Other	4	2.6
Death (90 days)	5	3.3
Death from liver failure	3	2.0
Cardiac death	2	1.3

As predictors for liver failure, degree of hypertrophy and measured growth rate both performed well, with AUC of 0.80 for degree of hypertrophy (95%, CI 0.62−0.99; p = 0.011), and 0.79 for growth rate (95% CI, 0.62−0.97; p = 0.015). Figure 5 shows the ROC curve for growth rate as a predictor of liver failure. The AUC for post-FLR/FLV to predict liver failure was modest at 0.71, but was not statistically significant (95% CI, 0.56−0.87; p = 0.076). As predictors of major complications, the performance of various parameters was similarly modest but also statistically significant. The AUCs to predict major complications were 0.65 for post-FLR/FLV (95% CI, 0.57−0.75; p = 0.002), 0.66 for degree of hypertrophy (95% CI, 0.57−0.76; p = 0.002), and 0.61 for growth rate (95% CI, 0.52−0.71; p = 0.032).

The AUCs for eGR were lower and not statistically significant at 0.58 (95% CI, 0.31−0.86; p = 0.484) for liver failure and 0.57 (95% CI, 0.47−0.67; p = 0.164) for major complications. When a comparison was performed using a permutation test, the predictive value of measured growth rate was superior to eGR for liver failure (AUC = 0.79 vs 0.58; p = 0.046).

DISCUSSION

Major liver resection in high-volume centers is now relatively safe with rates of perioperative mortality of 3% and major morbidity of 45%.[20] Although uncommon, liver insufficiency is still a major source of mortality and morbidity. Because Makuuchi and colleagues applied PVE to induce remnant hypertrophy in hilar cholangiocarcinoma in the 1980s,[21] PVE has been extended to treatment of hepatocellular carcinoma and liver metastases. It has been shown that PVE is safe and effective, and that it can allow some patients with borderline resectable disease to become resectable.[9,22-26]

Patients have variable hypertrophic response to PVE. The factors that affect hypertrophy are not well characterized, as study populations have been heterogeneous. Some studies have shown that the size of the FLR before PVE predicts the degree of hypertrophy.[27,28] Other possible factors include chronic liver disease,[22,29] diabetes,[30,31] and chemotherapy,[32,33] although these have not been consistently shown to be significant.[34-36] More recent studies have not found chemotherapy to be associated with poor growth.[11,27,37-39]

Portal vein embolization leads to hemodynamic changes and redistribution of hepatic growth factors

Table 3. Baseline and Treatment Characteristics for Patients With and Without Major Complications

	All patients	No major complications	Major complications	p Value
Total patients, n	153	109	44	
Age, y, median (IQR)	57 (50–65)	56 (50–66)	55 (50–65)	0.79
Males, n (%)	95 (62.1)	66 (60.6)	29 (65.9)	0.58
BMI, kg/m^2, median (IQR)	27.3 (24.7–30.5)	27.7 (24.8–30.8)	26.1 (24.5–28.9)	0.16
Histology, n (%)				
Colorectal metastases	137 (89.5)	97 (89.0)	40 (90.9)	1.00
Non–colorectal metastases	5 (3.3)	5 (4.6)	0	0.32
Hepatocellular carcinoma	6 (3.9)	4 (3.7)	2 (4.5)	1.00
Primary biliary carcinoma	5 (3.3)	3 (2.8)	2 (4.5)	0.63
Comorbidities, n (%)				
Diabetes	9 (5.9)	7 (6.4)	2 (4.5)	1.00
Moderate or severe steatosis	14 (9.2)	10 (9.2)	4 (9.1)	1.00
Cirrhosis	2 (1.3)	1 (0.9)	1 (2.3)	0.49
Chemotherapy within 6 mo, n (%)				
Any	126 (82.4)	86 (78.9)	40 (90.9)	0.10
5-FU	120 (78.4)	83 (76.1)	37 (84.1)	0.39
Oxaliplatin	58 (37.9)	34 (31.2)	24 (54.5)	0.01
Irinotecan	68 (44.4)	55 (50.5)	13 (29.5)	0.02
Bevacizumab	28 (18.3)	17 (15.6)	11 (25.0)	0.18
Hepatic arterial infusion pump FUDR	35 (22.9)	25 (22.9)	10 (22.7)	1.00
Operation, n (%)				
Right hemihepatectomy	93 (60.8)	65 (59.6)	28 (63.6)	0.72
Extended right hemihepatectomy	51 (33.3)	36 (33.0)	15 (34.1)	1.00
Left hemihepatectomy	4 (2.6)	4 (3.7)	0	0.33
Extended left hemihepatectomy	5 (3.3)	4 (3.7)	1 (2.3)	1.00
Days from PVE to post-PVE scan, median (IQR)	27 (20–33)	28 (21–33)	26 (19–31)	0.15
Volumetrics, mL, median (IQR)				
Pre-PVE FLV	1,636 (1,437–1,885)	1,631 (1,439–1,885)	1,714 (1,423–1,877)	0.84
Pre-PVE FLR	560 (473–678)	568 (482–678)	537 (466–676)	0.37
Pre-PVE FLR/FLV %	35.3 (29.8–40.1)	35.83 (30.35–40.22)	34.4 (29.1–38.2)	0.32
Post-PVE FLV	1,626 (1,443–1,846)	1,612 (1,454–1,821)	1,685 (1,426–1,856)	0.67
Post-PVE FLR	725 (628–884)	750 (637–905)	707 (599–778)	0.07
Post-PVE FLR/FLV, %	45.3 (39.7–50.4)	46.8 (40.6–51.3)	41.9 (38.5–46.4)	0.002
Degree of hypertrophy, %	9.64 (6.75–12.36)	10.64 (7.29–12.91)	7.94 (4.65–10.62)	0.001
Growth rate, % per week	2.48 (1.66–3.44)	2.62 (1.77–3.64)	2.26 (1.34–3.14)	0.03
eFLV	1,708 (1,485–1,946)	1,710 (1,493–1,945)	1,690 (1,437–1,952)	0.65
eGR, % per week	2.25 (1.41–3.28)	2.42 (1.47–3.31)	2.06 (1.04–3.06)	0.16

eFLV, estimated functional liver volume based on body surface area[12]; eGR, Estimated growth rate; FLR, future liver remnant; FLV, functional liver volume; FUDR, floxuridine; IQR, interquartile range; PVE, portal vein embolization.

that provide stimulus for hypertrophy of the remnant liver analogous to those that lead to liver regeneration after hepatectomy.[40] Traditionally, after PVE, the static measure of FLR as a percentage of total liver volume provides an estimate of the risk of post-hepatectomy liver failure and influences a surgeon's decision to proceed with resection. However, our data showed that the FLR volume in itself is not a good predictor of morbidity or liver failure. It has been shown that degree of hypertrophy correlates with post-hepatectomy outcomes[41]; however, it takes several weeks for degree of hypertrophy to become apparent. The measured growth rate is an early marker of the regenerative capacity of the liver remnant and can provide additional functional information beyond traditional, static measures of volume. Recently, Shindoh and colleagues showed that the rate of FLR growth, which they termed *kinetic growth rate*, has a better predictive value than degree of hypertrophy alone for postoperative

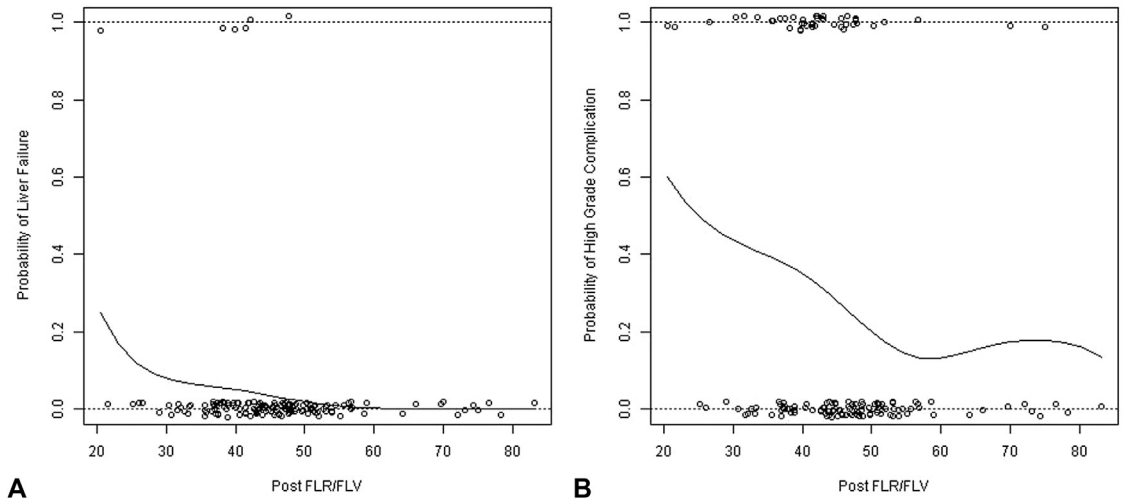

Figure 2. Nonparametric regression of post portal vein embolization future liver remnant (FLR)/functional liver volume (FLV) percent to predict (A) probability of liver failure, and (B) probability of major complications. A steeper slope indicates a stronger predictor.

outcomes.[11] In the current study, we found similar results, in that the speed of growth as well as the extent of growth correlated with post-hepatectomy liver failure. However, we found that degree of hypertrophy was a superior predictor for high-grade complications and liver failure, when compared with growth rate. Measured growth rate is still a useful index because it is an early marker that can support going forward with the procedure before the customary 4 to 6 weeks. A composite score using several volumetric parameters to more accurately predict liver failure would be desirable; however, our attempts to derive such a score using multivariate logistic regression failed to improve the prediction model. The likely explanation for this is that all of the volume-related variables are mathematically related, with a major contribution from the low rate of liver failure in this cohort. Although using major morbidity as one of the outcomes will increase the number of events for statistical analysis, our results showed that volumetric measures were only modest predictors for major morbidity.

Although the ability of volumetry to predict liver failure makes biologic sense, the mechanism of its correlation with major complications, the majority of which comprise intra-abdominal collections, biloma, and infection, is unclear. It is reasonable to speculate, however, that patients recovering from major abdominal surgery

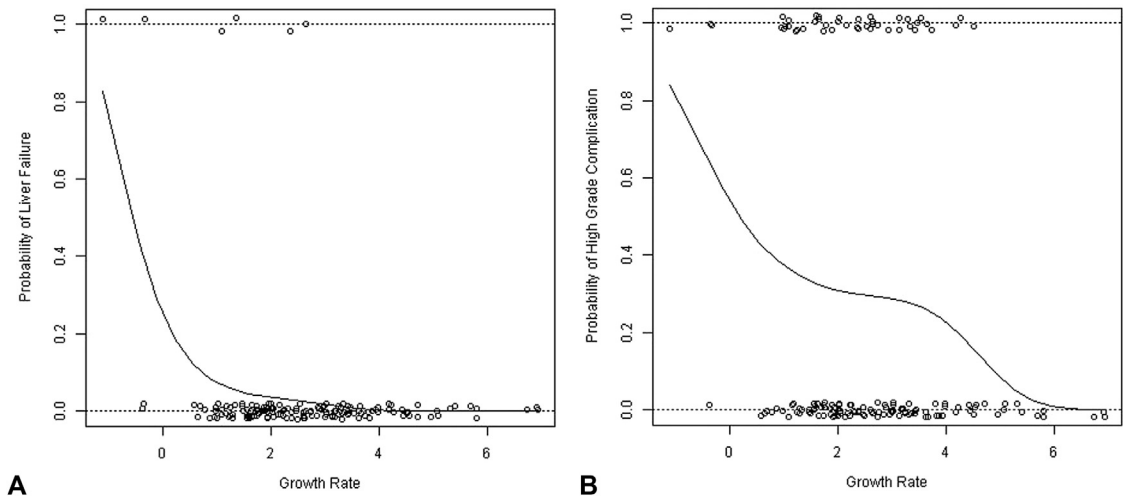

Figure 3. Nonparametric regression of measured growth rate to predict (A) probability of liver failure, and (B) probability of major complications. A steeper slope indicates a stronger predictor.

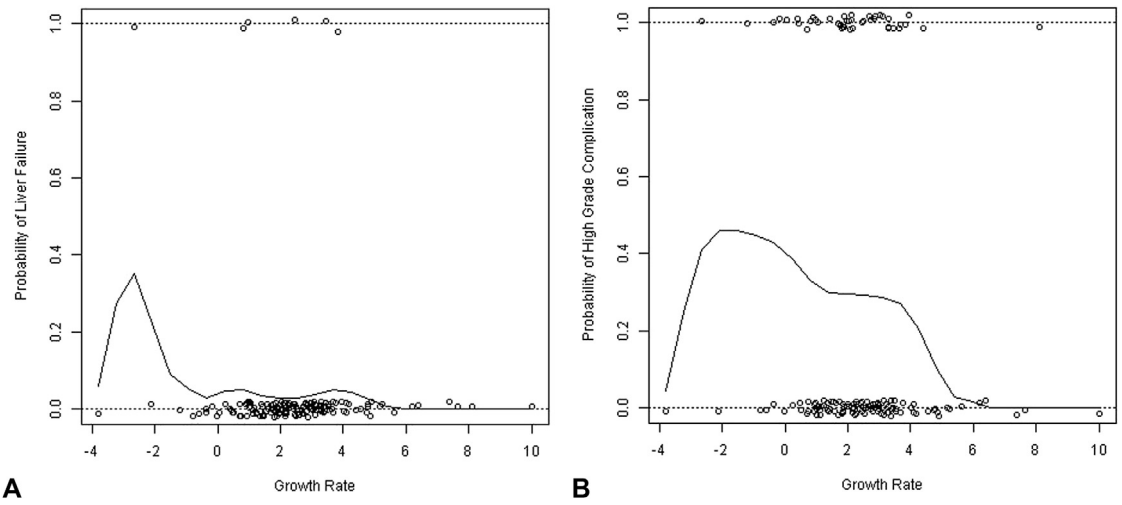

Figure 4. Nonparametric regression of estimated growth rate to predict (A) probability of liver failure, and (B) probability of major complications. A steeper slope indicates a stronger predictor.

with a poorly functioning liver would be at greater risk for a wide array of postoperative complications, in both absolute terms and severity.

In the current study, no patient with a growth rate >2.66% per week had liver failure develop. Although it would be useful to determine an absolute cutoff value above which a patient is relatively "safe" for surgery, the low incidence of liver failure in this cohort requires that we stop short of such a firm conclusion, pending confirmation of the results in future studies. Additionally, although early resection in patients who demonstrate rapid regeneration appears to be safe, it must be recognized that the number of data points based on CT scans obtained early after PVE was low, and such a recommendation is based on extrapolation from the available data. We found that growth rate correlated with liver failure better than it did with major complications, most likely because multiple factors contribute to postoperative morbidity. A meaningful cutoff value for complications was difficult to identify, as the predictive values for degree of hypertrophy and growth rate for complications were relatively poor (AUC = 0.66 and AUC = 0.61, respectively).

It has been proposed that an estimated FLR (or standardized FLR [sFLR]), calculated from body surface area[12,42] or weight[43] might be a superior measure of FLR, compared with computerized volumetry. Proponents of this approach cite as advantages less error in the presence of multiple tumors or biliary dilation, and more accurate measurement of functional volume in the presence of diseased liver parenchyma. We believe that accurate exclusion of nonparenchymal structures is technically feasible. In addition, sFLR formulas were developed and validated on patients without chronic liver disease and, therefore, might still overestimate the functional volume in patients with steatosis, cirrhosis, and chemotherapy-associated liver injury. When the sFLR formula[12] was applied to our cohort, the estimated sFLR was similar to our measured FLR, with a median of 1,708 mL vs 1,636 mL, IQR of 461 mL vs 448 mL. However, large differences were observed for volumes falling at extreme ends of the normal range. For the patient in our dataset with the smallest liver, sFLR overestimated the volume by 300 mL, and for the largest liver sFLR underestimated by 1,000 mL. An explanation for this discrepancy might lie in the method by which sFLR formula is derived

Table 4. Area Under the Receiver Operating Characteristic Curves for Growth Parameters to Predict Liver Failure and Major Complications

	Liver failure			Major complications		
Growth parameter	**AUC**	**95% CI**	**p Value**	**AUC**	**95% CI**	**p Value**
Post-PVE FLR/FLV %	0.71	0.56–0.87	0.076	0.65	0.57–0.75	0.002
DH	0.80	0.62–0.99	0.011	0.66	0.57–0.76	0.002
GR	0.79	0.62–0.97	0.015	0.61	0.52–0.71	0.032
eGR	0.58	0.31–0.86	0.484	0.57	0.47–0.67	0.164

AUC, area under the curve; DH, degree of hypertrophy; eGR, estimated growth rate; FLR, future liver remnant; FLV, functional liver volume; GR, growth rate; PVE, portal vein embolization.

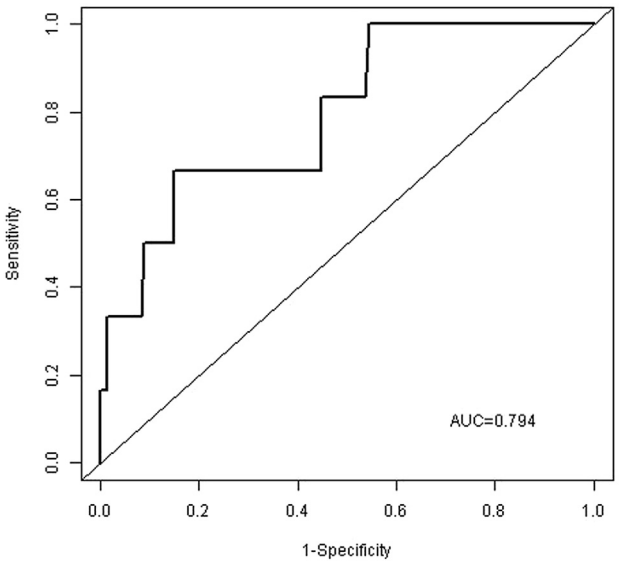

Figure 5. Receiver operating characteristic curve for growth rate as a predictor of liver failure. Area under the curve (AUC) = 0.794 (p = 0.015).

by regression ($r^2 = 0.46$), which predicts means but underestimates the variation among individual values. Although there are advantages to using the sFLR, such as speed and less inter-user variability, we believe that a measured FLR should remain the gold standard.

Shindoh and colleagues[11] reported a very high predictive value for liver failure using sFLR-based growth rate. We were unable to reproduce these results in the current study, which might be due to differences in patient populations and selection. Although the demographic characteristics of our patient populations were similar, we included patients with diagnoses other than colorectal metastases. The overall use of systemic chemotherapy was comparable, but the pattern of chemotherapy agents used was different. Our patients had a much higher rate of irinotecan (44% vs 15%) and lower rate of oxaliplatin (38% vs 80%) treatment. An important technical difference between these two studies is that we do not routinely embolize the portal vein branch to segment 4, specifically to avoid injury to the future remnant. For our patients with an extended right hepatectomy, which was 33.3% of our study population, the measured nonembolized liver volume is higher than the true post-resection liver remnant. This likely contributed to the observed higher pre-PVE volume (median 35.3%) and post-PVE volume (median 45.3%). Clinicians' concerns about the quality of the liver parenchyma might have also led to a lower threshold for embolization in our cohort.

Chemotherapy is associated with liver injury and, therefore, with a higher remnant volume requirement to prevent post-hepatectomy liver failure. Covey and colleaguges[37] showed that chemotherapy did not alter the overall growth of the FLR after PVE, and that PVE might even have a protective effect on the remnant liver against chemotherapy-related injury. More recently, we reported the benefit of post-PVE chemotherapy to protect against tumor growth between the time of PVE and hepatectomy.[44] The majority of patients in our study were pretreated with chemotherapy, often with prolonged courses and multiple agents, including the 44.4% who received irinotecan, known to be associated with steatohepatitis.[45] We have not found any increase in rates of liver failure or major complications in patients treated with chemotherapy. Despite the high-risk nature of many of our patients, the 3.9% liver failure rate and 3.3% overall mortality rate are comparable with those in the literature.[26,46]

This study is limited by its retrospective nature, with inherent selection bias and uncontrolled confounders. Only patients who proceeded to surgery were eligible, therefore, patients with very poor growth rates might have been excluded. A previous study from our institution showed that 19 of 74 (25.7%) patients undergoing PVE did not proceed to surgery.[10] Each patient in our current study had only a single post-PVE scan analyzed. A prospective study where serial scans are performed at set intervals after PVE would provide a more accurate growth trajectory. Current imaging technology allows detection of regeneration at 5 days after liver resection, so it is conceivable that similar changes would be measureable early after PVE.[47] Including such early data points would provide more accurate assessment of the growth rate and perhaps strengthen its predictive ability.

Although the volume of the FLR closely approximated the volume of the nonembolized lobe in patients undergoing a hemihepatectomy, the FLR of patients who underwent an extended right hepatectomy were underestimated because segment 4 was not embolized. We divided the liver based on embolization pattern rather than actual resection plane for the following reasons: attempting to predict the actual resection plane retrospectively would be associated with significant error; the focus of the study was on the liver growth rate after embolization, which was not affected by the extent of resection; a small proportion of patients had extended right hepatectomy; and the volume of segment 4 was relatively low. Although our methodology potentially influenced the predictive value of the FLR alone, it should not have an impact on the validity of growth rate as a predictor of liver failure, which measured the change in FLR. For example, our degree of hypertrophy was similar to those reported in the literature, which range from 8.7% to 13% at 4 to 6 weeks after PVE.[11,26,31,33,38]

The low incidence of liver failure posed a number of limitations on our analysis. With such a small number of events, adding or subtracting a single patient can alter the predictive value of the volumetrics considerably. However, the results of the current study were very similar to those of Shindoh and colleagues[11] with respect to the "safe" growth rate (2.66% per week in our study compared with 2.0% per week in their study). We, therefore, believe that this number very likely approximates the safe growth rate, although caution must be exercised and confirmation from other groups is necessary. The positive predictive value of any growth marker is also limited by the low incidence, and most patients with growth rates below this level will not have liver failure develop. One can also postulate that growth rate is most relevant when the final FLR is small; however, we were unable to stratify the growth rate according to the final size achieved because of the low event rate. Finally, a multivariate analysis on factors that predicted liver failure could not be performed. By contrast, the strengths of the study include the large cohort size derived from a well-established, prospectively maintained database.

CONCLUSIONS

Degree of hypertrophy and growth rate, measured after PVE, were both predictive of liver failure after resection. Traditional static measure of remnant volume is a poor guide to the safety of proceeding to surgery. Early surgery can be safe in patients who show an adequate growth rate. Although the optimum cutoff is yet to be determined, in this study no patient who achieved a growth rate >2.66% per week had liver failure develop. Therefore, we support use of this result as a guide. Growth parameters based on measured liver volume correlated better with outcomes than did those based on estimated liver volume.

Author Contributions

Study conception and design: Leung, Simpson, Araujo, Miga, Jarnagin

Acquisition of data: Leung, Simpson, Araujo, McAuliffe, Parada, Allen, D'Angelica, Kingham, DeMatteo, Fong, Jarnagin

Analysis and interpretation of data: Leung, Simpson, Gönen, Jarnagin

Drafting of manuscript: Leung, Simpson, Gönen, Jarnagin

Critical revision: Leung, Simpson, Araujo, Gönen, McAuliffe, Miga, Parada, Allen, D'Angelica, Kingham, DeMatteo, Fong, Jarnagin

REFERENCES

1. Fan ST, Lo CM, Liu CL, et al. Safety of donors in live donor liver transplantation using right lobe grafts. Arch Surg 2000; 135:336–340.
2. Kokudo N, Sugawara Y, Imamura H, et al. Tailoring the type of donor hepatectomy for adult living donor liver transplantation. Am J Transplant 2005;5:1694–1703.
3. 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.
4. Shoup M. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg 2003;7:325–330.
5. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997;26:1176–1181.
6. Soyer P, Roche A, Elias D, Levesque M. Hepatic metastases from colorectal cancer: influence of hepatic volumetric analysis on surgical decision making. Radiology 1992;184:695–697.
7. Hemming AW, Reed AI, Howard RJ, et al. Preoperative portal vein embolization for extended hepatectomy. Ann Surg 2003; 237:686–691; discussion 691–683.
8. Zorzi D, Laurent A, Pawlik TM, et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94:274–286.
9. Abdalla EK, Adam R, Bilchik AJ, et al. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1271–1280.
10. Correa D, Schwartz L, Jarnagin WR, et al. Kinetics of liver volume changes in the first year after portal vein embolization. Arch Surg 2010;145:351–354; discussion 354–355.
11. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. J Am Coll Surg 2013;216:201–209.
12. 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.
13. Brown KT, Brody LA, Decorato DR, Getrajdman GI. Portal vein embolization with use of polyvinyl alcohol particles. J Vasc Interv Radiol 2001;12:882–886.
14. Alyassin AM, Lancaster JL, Downs JH 3rd, Fox PT. Evaluation of new algorithms for the interactive measurement of surface area and volume. Med Phys 1994;21:741–752.
15. Martin RC 2nd, Jaques DP, Brennan MF, Karpeh M. Achieving RO resection for locally advanced gastric cancer: is it worth the risk of multiorgan resection? J Am Coll Surg 2002;194:568–577.
16. Balzan S, Belghiti J, Farges O, et al. The "50-50 criteria" on postoperative day 5. Ann Surg 2005;242:824–829.
17. Bowman AW, Azzalini A. Applied Smoothing Techniques for Data Analysis: The Kernel Approach with S-Plus Illustrations. Oxford: Oxford University Press; 1997.
18. Gönen M. Analyzing Receiver Operating Characteristic Curves with SAS. Cary, NC: SAS Institute Inc.; 2007.
19. Venkatraman ES, Begg CB. A distribution-free procedure for comparing receiver operating characteristic curves from a paired experiment. Biometrika 1996;83:835–848.
20. Jarnagin WR, Gönen 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 406–397.
21. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar

bile duct carcinoma: a preliminary report. Surgery 1990;107:521–527.
22. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237:208–217.
23. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg 2000;231:480–486.
24. Elias D, Ouellet JF, De Baere T, et al. Preoperative selective portal vein embolization before hepatectomy for liver metastases: long-term results and impact on survival. Surgery 2002;131:294–299.
25. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675–680; discussion 680–671.
26. Shindoh J, Tzeng CW, Aloia TA, et al. Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients. J Gastrointest Surg 2014;18:45–51.
27. de Baere T, Teriitehau C, Deschamps F, et al. Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. Ann Surg Oncol 2010;17:2081–2089.
28. Okabe H, Beppu T, Nakagawa S, et al. Percentage of future liver remnant volume before portal vein embolization influences the degree of liver regeneration after hepatectomy. J Gastrointest Surg 2013;17:1447–1451.
29. Cotroneo AR, Innocenti P, Marano G, et al. Pre-hepatectomy portal vein embolization: single center experience. Eur J Surg Oncol 2009;35:71–78.
30. Lee KC, Kinoshita H, Hirohashi K, et al. Extension of surgical indications for hepatocellular carcinoma by portal vein embolization. World J Surg 1993;17:109–115.
31. Imamura H, Shimada R, Kubota M, et al. Preoperative portal vein embolization: an audit of 84 patients. Hepatology 1999;29:1099–1105.
32. Beal IK, Anthony S, Papadopoulou A, et al. Portal vein embolisation prior to hepatic resection for colorectal liver metastases and the effects of periprocedure chemotherapy. Br J Radiol 2006;79:473–478.
33. Narita M, Oussoultzoglou E, Chenard MP, et al. Sinusoidal obstruction syndrome compromises liver regeneration in patients undergoing two-stage hepatectomy with portal vein embolization. Surg Today 2011;41:7–17.
34. Nanashima A, Sumida Y, Shibasaki S, et al. Parameters associated with changes in liver volume in patients undergoing portal vein embolization. J Surg Res 2006;133:95–101.
35. Nagino M, Nimura Y, Kamiya J, et al. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. Hepatology 1995;21:434–439.
36. 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.
37. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451–455.
38. Goere D, Farges O, Leporrier J, et al. Chemotherapy does not impair hypertrophy of the left liver after right portal vein obstruction. J Gastrointest Surg 2006;10:365–370.
39. Nafidi O, Desy D, Letourneau R, et al. Hypertrophy of the non-embolized liver after chemotherapy. HPB (Oxford) 2009;11:103–107.
40. Avritscher R, Duke E, Madoff DC. Portal vein embolization: rationale, outcomes, controversies and future directions. Expert Rev Gastroenterol Hepatol 2010;4:489–501.
41. Ribero D, Abdalla EK, Madoff DC, et al. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg 2007;94:1386–1394.
42. Ribero D, Amisano M, Bertuzzo F, et al. Measured versus estimated total liver volume to preoperatively assess the adequacy of the future liver remnant: which method should we use? Ann Surg 2013;258:801–807.
43. Chun YS, Ribero D, Abdalla EK, et al. Comparison of two methods of future liver remnant volume measurement. J Gastrointest Surg 2008;12:123–128.
44. Fischer C, Melstrom LG, Arnaoutakis D, et al. Chemotherapy after portal vein embolization to protect against tumor growth during liver hypertrophy before hepatectomy. JAMA Surg 2013;148:1103–1108.
45. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065–2072.
46. van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: a systematic review. Cardiovasc Interv Radiol 2013;36:25–34.
47. Simpson AL, Geller DA, Hemming AW, et al. Liver planning software accurately predicts post-operative liver volume and measures early regeneration. J Am Coll Surg 2014 Mar 27. pii: S1072–7515(14)00282-8. http://dx.doi.org/10.1016/j.jamcollsurg.2014.02.027. [Epub ahead of print].