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

Junichi Shindoh, MD, PhD[1], **Mark J Truty, MD, MSc**[1], **Thomas A Aloia, MD, FACS**[1], **Steven A Curley, MD, FACS**[1], **Giuseppe Zimmitti, MD**[1], **Steven Y Huang, MD**[2], **Armeen Mahvash, MD**[2], **Sanjay Gupta, MD**[2], **Michael J Wallace, MD**[2], and **Jean-Nicolas Vauthey, MD, FACS**[1]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center

[2]Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center

Abstract

Background—Standardized future liver remnant (sFLR) volume and degree of hypertrophy after portal vein embolization (PVE) have been recognized as significant predictors of surgical outcomes after major liver resection. However, regeneration rate of the FLR after PVE varies among individuals and its clinical significance is unknown.

Study Design—Degree of hypertrophy at initial volume assessment divided by number of weeks elapsed after PVE was defined as the kinetic growth rate (KGR). In 107 consecutive patients who underwent liver resection for colorectal liver metastases with a sFLR volume of greater than 20%, the ability of the KGR to predict overall and liver-specific postoperative morbidity and mortality was compared with sFLR volume and degree of hypertrophy.

Results—Using receiver operating characteristic analysis, the best cut-off values for sFLR volume, degree of hypertrophy, and KGR for predicting postoperative hepatic insufficiency were estimated as, respectively, 29.6%, 7.5%, and 2.0% per week. Among these, KGR was the most accurate predictor (area under the curve, 0.830 [0.736-0.923]; asymptotic significance, 0.002). KGR of less than 2% per week vs. 2% per week correlate with rates of hepatic insufficiency (21.6% vs. 0%, p = 0.0001) and liver-related 90-day mortality (8.1% vs. 0%, P=0.04). The predictive value of KGR was not influenced by sFLR volume or the timing of initial volume assessment when evaluated within 8 weeks after PVE.

Conclusions—KGR is a better predictor of postoperative morbidity and mortality after liver resection for small FLR than conventional measured volume parameters (sFLR volume and degree of hypertrophy).

Correspondence address: Jean-Nicolas Vauthey, MD, Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcomb Boulevard, Unit 1484; Houston, TX 77030, USA; Telephone: 713-792-2022; Facsimile: 713-745-1921, jvauthey@mdanderson.org.

Introduction

For patients with colorectal liver metastases (CLM), the introduction of effective systemic therapies and an increase in the utilization of major hepatectomy have led to significant improvements in long-term survivals during the past decade.[1] Our group has utilized and reported various strategies to expand resectability for patients with CLM including perioperative chemotherapy and staged surgical procedures with the use of portal vein embolization (PVE).[2, 3] The trophic effects of pre-operative PVE on the future liver remnant (FLR) allows for safe preservation of hepatic reserve in order to decrease the incidence of postoperative liver failure and death after extended liver resections, which is particularly important in patients with chemotherapy associated liver disease.[4]

As the techniques and indications for PVE have evolved over time, numerous groups have attempted to more accurately predict postoperative outcomes on the basis of PVE-induced preoperative radiographic volume changes.[5] As part of our experience with PVE, we have observed significant variability in the rate of growth of the liver remnant after PVE. In this study, we sought to clarify this clinical observation by determining the relationship between postoperative outcome and kinetic growth rate (KGR), defined as the increase in FLR volume from baseline to first post-PVE volume assessment divided by length of time (weeks) between PVE and first post-PVE volumetry.

Patients and Methods

The Institutional Review Board of The University of Texas, MD Anderson Cancer Center, approved this study protocol (PA12-0225). From a prospective hepatobiliary database maintained by the Department of Surgical Oncology, 194 consecutive patients who underwent right PVE before planned right hemihepatectomy or extended right hepatectomy for small FLR in patients with colorectal metastases between January 1993 and March 2012 were identified.

Of these 194 patients, 44 patients who were unable to proceed to surgery due to progression of disease (n = 30), insufficient regeneration of FLR (n = 5), or other medical issues (n = 9) and 16 patients who were unresectable at laparotomy were excluded from this study. To explore the effect of KGR, patients who did not meet our current minimal FLR volume criteria (>20% of standardized liver volume) [6-8] (n = 19) or who did not undergo initial post-PVE radiographic volume assessment within 8 weeks after PVE (n = 8) were also excluded from the analysis. Thus the remaining 107 patients constituted the current study cohort.

Pre-PVE liver volumetry, calculation of sFLR volume, and PVE

All patients with potentially resectable disease underwent preoperative liver volumetry based on computed tomography (CT) imaging, and sFLR volume was estimated according to the previously reported method.[9] Enhanced CT scans were performed with a multidetector row CT, 4, 16, or 64 slices (Light-Speed; GE Healthcare, Piscataway, NJ), using a triphasic liver protocol or single-phase technique at 2.5 – 5 mm thick slices. The liver volumes were determined by loading the CT images onto an Advantage Workstation 4.1 (GE Medical Systems, Milwaukee, WI). Standardized liver volume was calculated using the following formula: $SLV = -794.41 + 1267.28 \times$ body surface area (m^2).[10] PVE was considered when sFLR was less than 20% in patients with normal liver, or less than 30% in patients with evidence of fibrosis or severe liver injury.[6, 7, 11] All embolizations were performed by the ipsilateral percutaneous transhepatic approach using tris-acryl microspheres ranging in size from 100-700 microns and coils. The right PVE was

specifically expanded to segment IV branches when extended right hepatectomy was considered.[12-15]

Post-PVE liver volumetry and calculation of DH and KGR

Initial post-PVE liver volume assessments were performed with 3-dimensional CT volumetry 2- to 8 weeks after PVE. Degree of hypertrophy (DH) was defined as the percentage point difference between the sFLR volume before and after PVE. The kinetic growth rate (KGR) was calculated by the following formula: KGR = DH at first post-PVE volume assessment (%) ÷ time elapsed since PVE (weeks) at first post-PVE volume assessment. If hypertrophy at the first post-PVE volume assessment was insufficient (i.e., sFLR volume less than 20% in patients with normal liver or sFLR volume less than 30% in patients with injured liver), serial radiographic volumetric assessments were performed and systemic therapy was administered if applicable until the sFLR volume was sufficient to permit resection.

Definitions of outcomes

Postoperative complications were classified using standard criteria, and major complications were defined as grade III or higher complications.[16] Postoperative hepatic insufficiency was defined as a peak total bilirubin level greater than 7mg/dL and/or typical clinical manifestations of hepatic insufficiency, including massive ascites or encephalopathy.[17] The death from liver failure was calculated at 90 days after surgical resection.

Comparison of volume parameters with respect to predicting postoperative hepatic insufficiency, morbidity, and mortality

The performance of sFLR volume, DH, and KGR in predicting hepatic insufficiency was assessed using receiver-operating characteristics (ROC) analysis. The accuracy of each parameter in discriminating patients with and without postoperative hepatic insufficiency was assessed by calculating the area under the curve (AUC) and the asymptotic significance level of each curve compared to the diagonal reference line (AUC=0.500). Using the best cut-off values determined by the ROC analysis, rates of major complications, hepatic insufficiency, and 90-day mortality were compared amongst patients.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (ver19.0. SPSS Inc., IL, USA). Median and ranges of continuous data were compared using the Mann-Whitney U test. Categorical data were compared using Pearson's chi-squared test or Fisher's exact test as appropriate.

Results

Patient characteristics

Baseline characteristics of the 107 studied patients are summarized in Table 1. Right PVE was performed in 40 (37.4%) patients and it was extended to segment IV branch in 67 (62.6%) patients. Of note, 89.7% of the 107 patients included in this study had some histopathological changes in the nontumoral liver, with 92.3% of these patients having received 5-fluorouracil or capecitabine based neoadjuvant chemotherapy.

Post-PVE liver hypertrophy

Table 2 summarizes volume measurements before and after PVE. Initial volume assessments were performed at a median of 30 days after PVE. Significant increases in both FLR volume and sFLR volume ($P < 0.0001$ vs. pre-PVE) were apparent at the time of first

post-PVE volume assessment with a median DH of 10.1% and KGR of 2.4% per week. Ninety-six patients (89.7%) proceeded to surgery at this point, while 11 (10.3%) patients in whom sFLR volumes were not sufficient for resection underwent additional waiting time (median, 100 days; range, 56 – 254 days) with serial radiographic observation until sFLR volume reached the criteria for resection (ie, sFLR>20%).[18] We found that the KGR was significantly higher for patients who were able to proceed to resection after first post-PVE volume assessment compared to those who required additional waiting time prior to meeting resection criteria, 2.5% per week (range, 0.2-9.4) versus 1.5% per week (range, 0.2-2.7), (P = 0.0056) (Table 3). Among patients with a KGR greater than 2.0% per week, only 4.4% (3/68) required additional waiting time to achieve an acceptable sFLR volume, whereas among patients with a KGR less than 2.0% per week, 20.5% (8/39) required additional waiting time (P = 0.0001).

Regarding the difference between right PVE and right PVE + segment IV, latter procedure showed, higher final standardized volume (25.4% vs. 20.5%, p=0.006), DH (9.5% vs. 6.2%, p=0.07), and KGR (2.3 %/week vs. 1.4%/week, p=0.02) of segment II+III, as reported previously.[15]

Background clinical factors and liver hypertrophy

Influence of background factors on final FLR, DH, and KGR were also investigated regarding patient age, gender, presence of diabetes, BMI, liver fibrosis, steatosis or steatohepatitis, sinusoidal injury, chemotherapy duration, and types of chemotherapy regimens. Among these, presence of diabetes was associated with lower KGR (1.3 %/week vs. 2.6 %/week, p=0.003) and lower DH (5.9% vs. 11.6%, p=0.02). And severe sinusoidal injury was also associated with lower KGR (1.2 %/week vs. 2.5 %/week, p=0.04). In the current population (92.3% received preoperative chemotherapy and 47.9% of them were treated with > 12 weeks of preoperative chemotherapy), no association with duration of chemotherapy or type of chemotherapy regimen was noted.

Postoperative complications, hepatic insufficiency, and mortality

All patients underwent resection without significant intraoperative events. The overall complication rate was 48.6% (55/107), and major complications were observed in 22.4% (24/107) of the cases. The postoperative hepatic insufficiency rate was 7.4% (8/107) and the rate of death from liver failure was 2.8% (3/107).

Accuracy of measured volume parameters for predicting postoperative hepatic insufficiency

ROC analysis of the 3 tested variables revealed that KGR was the best predictor of postoperative hepatic insufficiency (AUC, 0.830; 95% CI, 0.736-0.923; asymptotic significance level, P = 0.002) (Figure 1). Based on the results of ROC analysis, the best cut-off values for sFLR volume, DH, and KGR to predict postoperative hepatic insufficiency were 29.6%, 7.5%, and 2.0% per week, respectively. In comparison of diagnostic power of these variables, KGR <2.0% per week showed the highest accuracy (81%) with sensitivity of 100% and specificity of 71% in predicting postoperative hepatic insufficiency (Table 4).

Accuracy of measured volume parameters for predicting postoperative morbidity and mortality

As shown in Figure 2, rates of major complications, hepatic insufficiency, and 90-day liver failure death were well predicted by use of cut-off values determined by the ROC analysis. Among patients with a KGR of at least 2.0% per week, there were no instances of postoperative hepatic insufficiency or liver failure death within 90 days. In contrast, among

those patients with a KGR of less than 2.0% per week, rates of hepatic insufficiency and 90-day liver failure death were 21.6% and 8.1%, respectively.

When the discriminatory power of KGR was compared between the patients who underwent initial CT assessment within 4 weeks after PVE and at 5-8 weeks after PVE, rates of postoperative hepatic insufficiency were 24% for KGR <2.0 % per week vs. 0% for KGR ≥ 2.0% per week ($P = 0.006$) in patients who underwent initial CT within 4 weeks after PVE, and 20% for KGR <2.0 % per week vs. 0% for KGR ≥ 2.0 % per week ($P = 0.02$) in patients who underwent initial volume assessment at 5-8 weeks after PVE (Figure 3A).

In addition, a subanalysis was performed in which the study population was stratified into 2 groups: patient with a sFLR volume of 20% to 30% and patients with sFLR volume greater than 30% (Figure 3B). In both groups, rates of hepatic insufficiency were higher among patients with a KGR less than 2.0% per week even after adjusting for similar sFLR volumes. This difference was markedly clinically significant, particularly in those patients with marginal sFLR volumes (i.e., 20% - 30%).

Discussion

In this study, we analyzed a novel dynamic measure for post-PVE FLR volume, the kinetic growth ratio (KGR). The analysis indicates that in patients undergoing major hepatectomy for colorectal liver metastases, KGR predicts postoperative hepatic insufficiency more effectively than the conventional measures, sFLR volume and DH. In addition, a KGR of at least 2.0% per week is protective of hepatic complications and liver failure related death. In patients without cirrhotic liver disease, hepatic insufficiency is a strong predictor of death from liver failure.[17, 18] The current study confirms previous studies indicating that approximately one third of patients with postoperative hepatic insufficiency eventually develop liver failure.[17, 18]

With the increasing frequency of complex and extensive procedures for patients pretreated with chemotherapy for colorectal liver metastases, the assessment of sFLR volume has become critical in determining which patients are most likely to benefit from PVE.[2, 3, 19-22] The trophic effects of PVE are specifically beneficial in patients with anticipated marginal sFLR volumes and those with liver injury due to modern systemic therapies.[11, 23, 24] Conventionally, outcomes of liver resection have been predicted mainly by static volumetric assessment of the preoperative sFLR volume.[6, 11, 18, 25, 26] We previously described the minimal necessary sFLR volume as greater than 20% for patients with normal livers, greater than 30% for patients with extensive preoperative chemotherapy or with histopathologic injuries, and greater than 40% for patients with cirrhosis.[4] Although these sFLR cutoffs are useful guide, they do not consistently predict surgical outcome.[27, 28]

For these reasons, we further evaluated the degree of hypertrophy (DH) and showed that a DH of greater than 5 percentage points after PVE along with an sFLR volume of greater than 20% predicted surgical outcomes with high specificity and sensitivity.[29] In this earlier work looking at the steady-state phase of liver growth after PVE, we found that hepatic dysfunction was more common in patients with a small sFLR volume, regardless of DH, and in those patients with a low DH, regardless of sFLR volume. These findings suggested that assessment of the unique patient-specific kinetics of post-PVE liver growth may contribute additional prognostic information beyond that provided by traditional volumetric evaluation in patients undergoing PVE before hepatic resection. The limitation of DH is that it only considers total remnant volume increase from PVE to final CT regardless of the time duration necessary to achieve this volume increase. Although typically most patients at our institution undergo post-PVE volumetry approximately 4 weeks after PVE,

the time from PVE to initial post-PVE volume assessment varies among individual patients for a variety of reasons. Degree of hypertrophy alone provides no information about such specific time interval kinetics, and the KGR appears to provide a useful estimation of individual regeneration curves after PVE.

Previous studies indicated that the remnant liver continues to grow when followed over a long duration of time (months) with only a fraction (25%) of the total possible liver growth being achieved within 30 days post-PVE.[30] Therefore, it has been hypothesized that if inadequate growth occurs after the first post-PVE volumetry assessment, patients can be reassessed later and their perioperative morbidity would be equivalent if they eventually reach adequate remnant volume.[29] In the current study, however, the 10% of patients who had not achieved an adequate sFLR volume at the time of initial post-PVE volume assessment showed higher rates of hepatic insufficiency even after achieving our current criteria of sFLR >20% prior to surgery that was well predicted by KGR (Table 4 & Figure 4). Furthermore, KGR completely predicted both postoperative hepatic insufficiency and mortality from liver failure even when the currently accepted sFLR volume criteria failed to discriminate postoperative outcomes.

The limitations of this study include its retrospective nature and selected population. However, the study is based on prospectively collected data, and the patients were treated using a similar approach with respect to PVE and sFLR volume.[4, 6, 12, 18] Another limitation is the timing of initial liver volume evaluation after PVE. Earlier studies reported that hypertrophy of the remnant liver follows a non-linear kinetic profile with rapid growth during the first 4 weeks. [29] However, the 2% cut off per week proposed in this study predicted postoperative hepatic insufficiency not only when measured within 4 weeks but also measured between 5-8 weeks after PVE. This suggests that KGR can be used as a reliable volumetric measure at least up to 8 weeks after PVE. Regarding the background factors affecting liver regeneration, the current study indicates that presence of diabetes or severe sinusoidal injury may be associated with impaired initial growth of the liver. However, because most patients included in received preoperative chemotherapy, additional studies investigating the effect of preoperative chemotherapy on liver regeneration are needed.

In conclusion, we present a novel dynamic measure for volume analysis after PVE that predicts surgical outcome. KGR is highly predictive of postoperative hepatic insufficiency in patients undergoing major liver resection for colorectal liver metastases. It provides additive information to the conventional static measure of post-PVE changes (sFLR volume), improving patient selection and outcomes.

Acknowledgments

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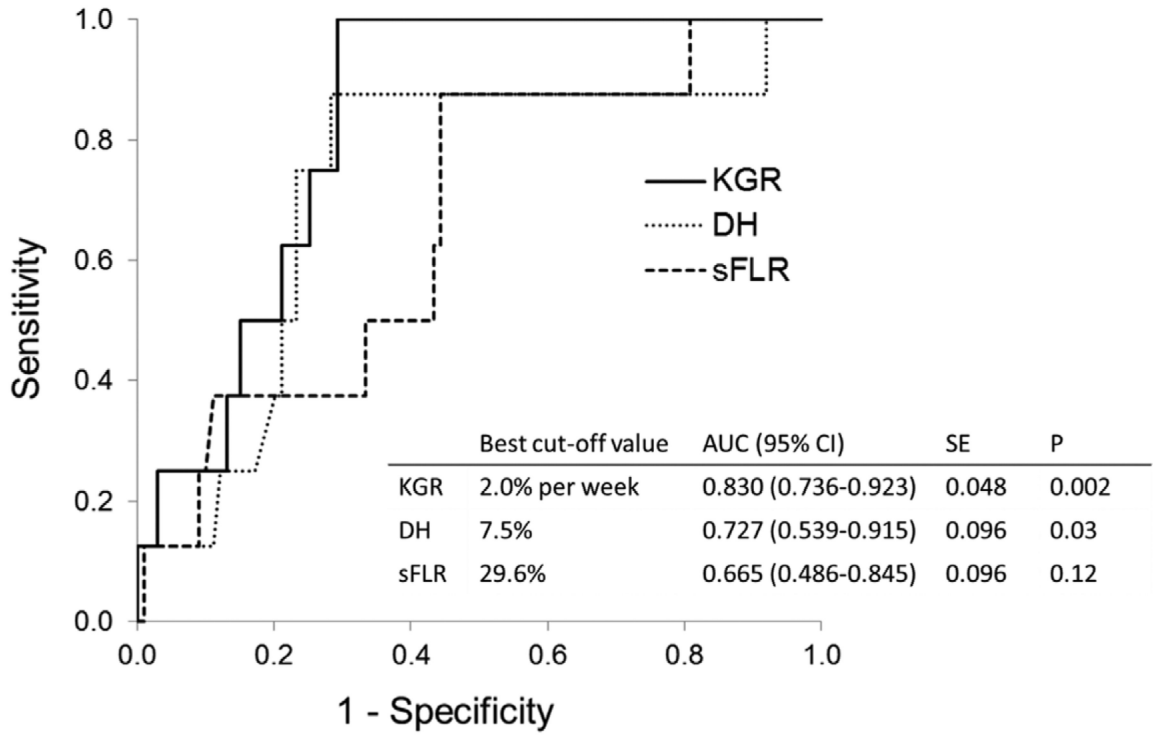
Figure 1.
Receiver operating characteristics curves for measured volume parameters in the prediction of postoperative hepatic insufficiency. sFLR, standardized future liver remnant; DH, degree of hypertrophy; and KGR, kinetic growth rate, defined as DH at first volume assessment after portal vein embolization (PVE) divided by weeks between PVE and first post-PVE volume assessment. AUC, area under the curve; CI, confidence interval; SE, standard error; p values represent asymptotic significance (null hypothesis, AUC = 0.500).
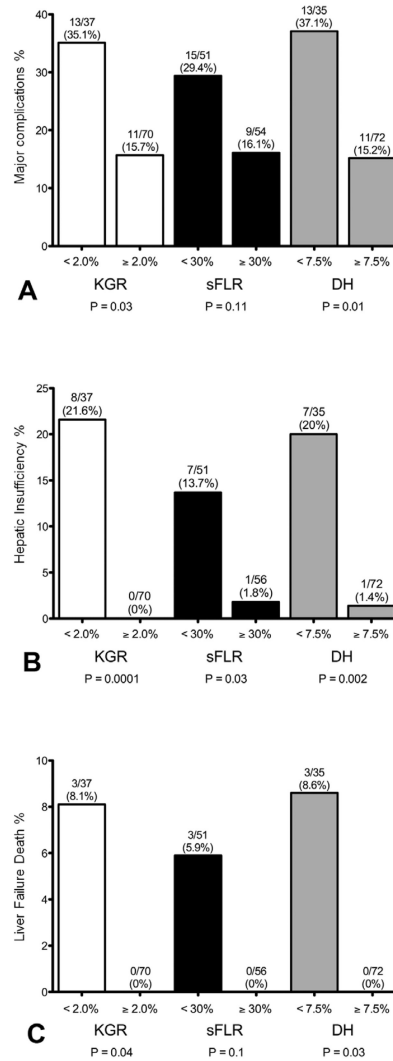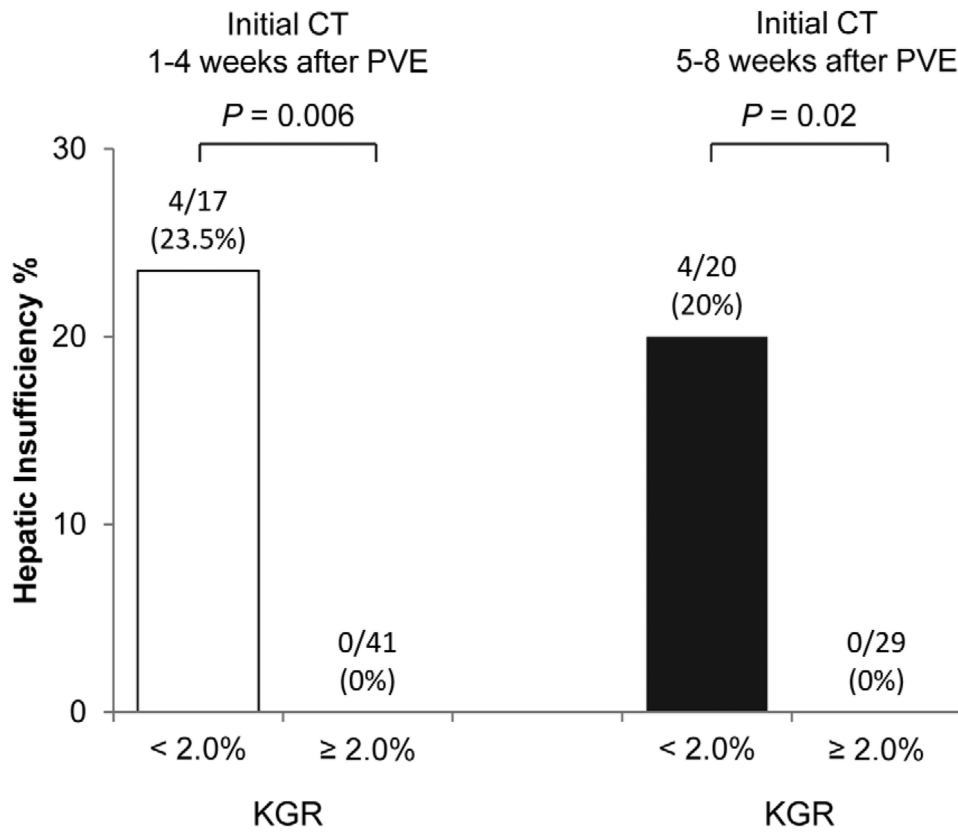
Figure 2.
Rates of (A) major complications, (B) hepatic insufficiency, and (C) 90-day liver-related mortality based on best cut-off values determined with receiver operating characteristics analysis. DH, degree of hypertrophy; KGR, kinetic growth rate, defined as DH at first volume assessment after PVE divided by weeks between PVE and first post-PVE volume assessment; PVE, portal vein embolization; sFLR, standardized future liver remnant.
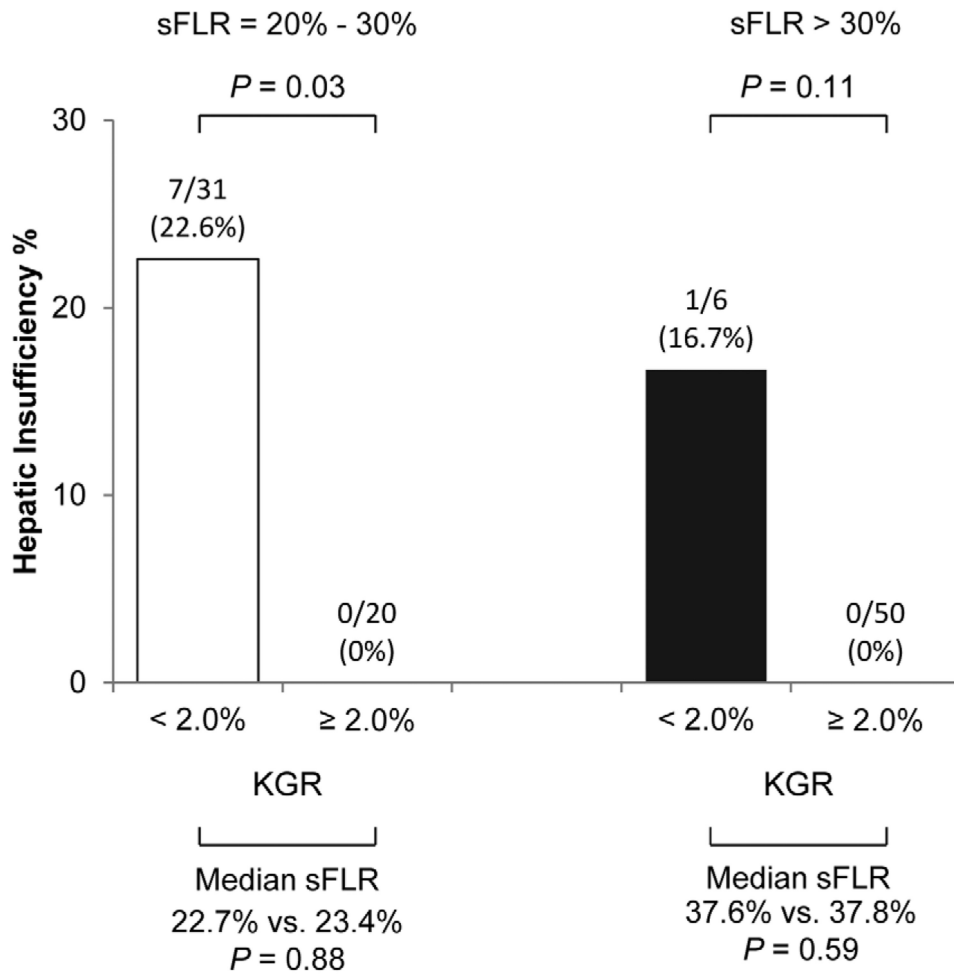
Figure 3.
Rates of hepatic insufficiency according to kinetic growth rate by timing of (A) initial volume assessment and (B) standardized future liver remnant volume. KGR, kinetic growth rate; PVE, portal vein embolization; sFLR, standardized future liver remnant.
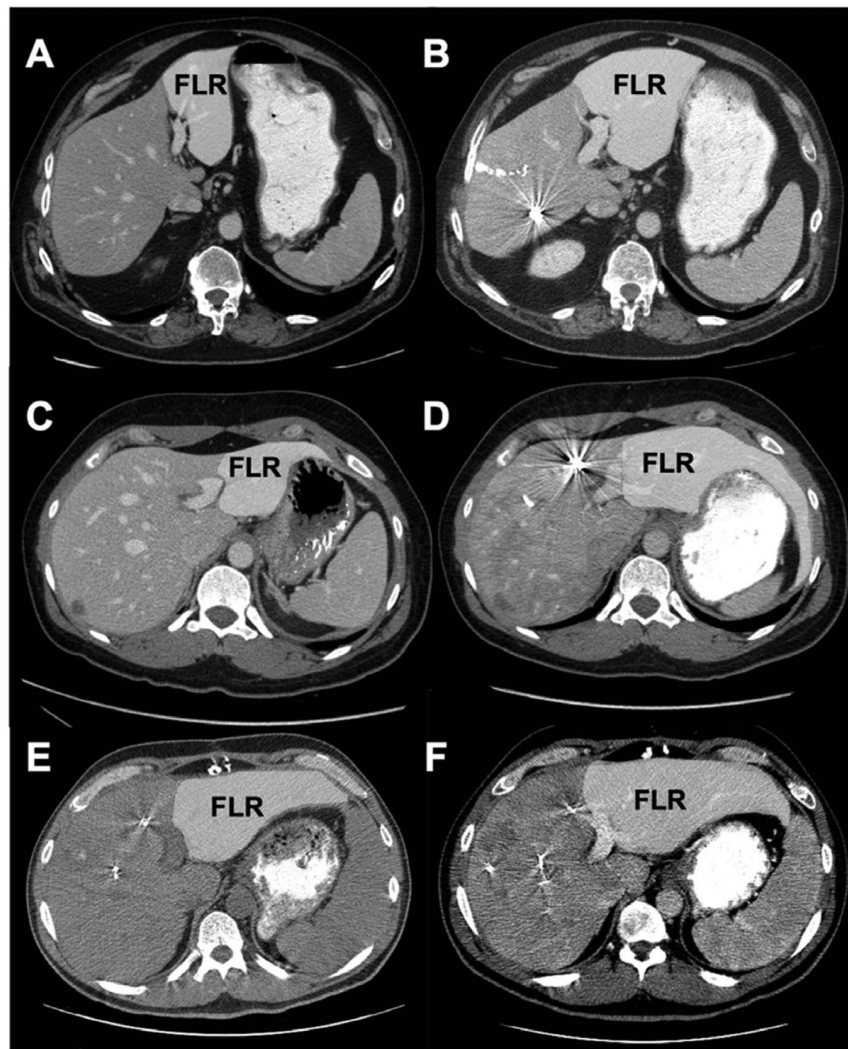
Figure 4.
Examples of the clinical utility of kinetic growth rate (KGR). All patients had future liver remnant (FLR) volume 30% and degree of hypertrophy (DH) 7.5% (suggested eligibility criteria for resection); however, KGR was a more accurate predictor of outcome. (A and B) 60-year-old man. (A) On the basis of the initial CT scan, standardized FLR volume (sFLR) was estimated at 9%. (B) Final CT 35 days after right portal vein embolization (PVE) extended to segment IV indicated an sFLR volume of 33%, DH of 24%, and KGR of 4.8% per week. The patient had an uneventful postoperative course. (C and D) 37-year-old woman. (C) On the basis of the initial CT scan, sFLR volume was estimated at 15%. (D) Final CT 35 days after right PVE extended to segment IV indicated an sFLR volume of 30%, DH of 15%, and KGR of 3.0% per week. The patient had an uneventful postoperative course. (E and F) 43-year-old man. (E) On the basis of the initial CT scan, sFLR volume was estimated at 23%. (F) Final CT 70 days after right PVE extended to segment IV (required additional waiting time to attain adequate remnant volume) indicated an sFLR volume of 31%, a DH of 8%, and a KGR of 0.3% per week (determined after first CT 28 days after PVE). The patient died of postoperative liver failure.

Table 1
Baseline Characteristics of Study Population (n = 107)

Age, y, median (range)	54 (34-76)
Males, n (%)	75 (70.9)
Diabetes, n (%)	7/103 (6.8)
BMI, kg/m^2, median (range)	25.6 (17.1 - 40.1)
ASA score 3, n (%)	85/103 (82.5)
Nontumoral liver pathology, n (%)	
None	77/95 (81.1)
Steatosis >30% or steatohepatitis [*]	6/99 (6.1)
Fibrosis (F1-4) [†]	8/101 (7.9)
Cirrhosis (F5-6) [†]	0/101 (0)
Sinusoidal injury [‡]	8/96 (8.3)
Type of PVE, n (%) [§]	
RPVE	40/107 (37.4)
RPVE extended to segment IV	67/107 (62.6)
5-FU or capecitabine based preoperative chemotherapy, n (%)	
Any	96/104 (92.3)
>12 wk duration	46/104 (44.2)
Oxaliplatin [§]	83/104 (79.8)
Irinotecan [§]	16/104 (15.4)
Bevacizumab	72/104 (69.2)
Cetuximab or Panitumumab	3/104 (2.9)

When 2 numbers are listed, the numerator is the number of patients with the characteristic and the denominator is the number of patients for whom information about this characteristic was available. Values in parentheses are percentage unless indicated otherwise.

[*] Kleiner score 4 or greater.[31]

[†] Fibrosis score according to Ishak et al.[32]

[‡] Rubbia-Brandt score 2-3 (moderate to severe).[33]

[§] Three patients had history of both FOLFOX and FOLFIRI.

BMI, body mass index; ASA, American Society of Anesthesiology; RPVE, right portal vein embolization.

Table 2

Measures of Future Liver Remnant Volume before and after Portal Vein Embolization

	Baseline measurement, median (range)	Initial post-PVE measurement (<8 week after PVE), median (range)	Final post-PVE measurement before surgery, median (range)
No. of days after PVE	0	30 (14 - 54)	31 (14 - 254)
FLR volume, mL	331 (148 - 927)	486 (257 - 1187)	497 (256 - 1186)
sFLR volume, %	20.1 (9.5 - 57.8)	29.4 (20.1 - 75.1)	31.2 (20.1 - 75.1)
DH, %	-	10.1 (0.1 - 39.9)	10.8 (0.1 - 39.9)
KGR, % per week	-	2.4 (0.2 - 9.4)	-

Eleven patients (10.3%) required additional waiting time at this point due to insufficient volume increase.

FLR, future liver remnant; sFLR, standardized FLR; DH, degree of hypertrophy; KGR, kinetic growth rate, defined as DH per week.

Table 3

Outcomes According to Whether the Standardized Future Liver Remnant Volume was Adequate at Initial Post-Portal Vein Embolization Volume Assessment

	Adequate sFLR Volume at Initial Assessment (n = 96)	Inadequate sFLR Volume at Initial Assessment (n = 11)	p Value
Any complication, n (%)	44/96 (45.8)	8/11 (72.3)	0.12
Major complication, n (%)	20/96 (20.8)	4/11 (36.4)	0.26
Peritoneal fluid collection	5/96 (5.2)	0/11 (0)	0.98
Bile leak	6/96 (6.3)	0/11 (0)	0.87
Abscess	1/96 (1.0)	0/11 (0)	0.19
Hepatic insufficiency	5/96 (5.2)	3/11 (27.3)	0.035
Ileus	1/96 (1.0)	0/11 (0)	0.19
Acute cardiac failure	1/96 (1.0)	1/11 (9.1)	0.49
Respiratory failure	1/96 (1.0)	0/11 (0)	0.19
90-day liver failure death, n (%)	2/96 (2.1)	1/11 (9.1)	0.28
Time from PVE to final CT, d, median (range)	30 (14-52)	100 (56-254)	<0.0001
Final sFLR volume, %, median (range)	31.9 (20.1-75.1)	28.3 (20.6-41.9)	0.21
Final DH, %, median (range)	10.9 (1-39.9)	6.8 (0.1-23.7)	0.30
KGR, % per wk, median (range)	2.5 (0.2-9.4)	1.5 (0.2-2.7)	0.0056

When 2 numbers are listed, the numerator is the number of patients with the characteristic and the denominator is the number of patients for whom information about this characteristic was available. Values in parentheses are percentage unless indicated otherwise.

CT, computed tomography; DH, degree of hypertrophy; KGR, kinetic growth rate; PVE, ; sFLR,

Table 4

Diagnostic Characteristics of Kinetic Growth Rate, Degree of Hypertrophy, and Standardized Future Liver Remnant Volume to Predict Postoperative Hepatic Insufficiency

	KGR <2.0% per wk	DH <7.5%	sFLR <30%
Sensitivity, n (%)	8/8 (100)	7/8 (88)	7/8 (88)
Specificity, n (%)	70/99 (71)	71/99 (72)	55/99 (56)
PPV, n (%)	8/37 (22)	7/35 (20)	7/51 (14)
NPV, n (%)	70/70 (100)	71/72 (99)	55/56 (98)
Accuracy, n (%)	87/107 (81)	78/107 (73)	62/107 (58)
LR+	3.4	3.1	2.0
LR−	0.0	0.2	0.2

KGR, kinetic growth rate; DH, degree of hypertrophy; sFLR, standardized future liver remnant volume; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio for positive test; LR−, likelihood ratio for negative test.