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Prediction of remnant liver hypertrophy ratio after preoperative portal vein embolization

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Short title: Prediction of hypertrophy ratio after PVE

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ABSTRACT

Background

Portal vein embolization (PVE) is considered to improve the safety of major hepatectomy. Various conditions might affect remnant liver hypertrophy after PVE. The aim of the present study was to clarify the factors that affect remnant liver hypertrophy and to establish a prediction formula for the hypertrophy ratio.

Methods

Fifty-nine patients who underwent preoperative PVE for cholangiocarcinoma (39 patients), metastatic carcinoma (10 patients), hepatocellular carcinoma (8 patients), and other diseases (2 patients) were enrolled in this study. For the prediction of the hypertrophy ratio, the prediction formula was set up with step-wise multiple regression analysis using the following parameters: age; gender; future liver remnant ratio to total liver (FLR%); plasma disappearance rate of indocyanine green (ICGK); platelet count; prothrombin activity; serum albumin; serum total bilirubin at the time of PVE and the maximum value before PVE (Max Bil); and history of cholangitis, diabetes mellitus, and chemotherapy.

Results

The mean hypertrophy ratio was 28.8%. The following 5 parameters were detected as predictive factors: age ($P = 0.015$), FLR% ($P < 0.001$), ICGK ($P = 0.112$), Max Bil ($P < 0.001$), and history of

chemotherapy ($P = 0.007$). The following prediction formula was calculated: $101.6 - 0.78 \times \text{Age} - 0.88 \times \text{FLR}\% + 128 \times \text{ICGK} - 1.48 \times \text{Max Bil (mg/dL)} - 21.2 \times \text{Chemotherapy}$. The value obtained using this formula significantly correlated with the actual value ($r = 0.72$, $P < 0.001$). A 10-fold cross validation also showed significant correlation ($r = 0.62$, $P < 0.001$), and the hypertrophy ratio below 20% was predictable with 100% sensitivity and 90.9% specificity. Moreover, technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin scintigraphy showed significantly less increase in the uptake ratio of the remnant liver in patients with prediction values below 20% than in those with values above 20% (6.8% vs. 20.8%, $P = 0.030$).

Conclusions

This prediction formula can predict the hypertrophy ratio after PVE, which may provide a new therapeutic strategy for major hepatectomy.

Key words

Portal vein embolization · Hypertrophy ratio · Prediction · Major hepatectomy · Associating liver partition and portal vein ligation for staged hepatectomy

Introduction

Liver resection is usually the only radical therapy for primary and metastatic liver tumor except for liver transplantation. Although liver surgery has become much safer because of improved diagnostic imaging, surgical procedures, and perioperative management during the past decades [1], high mortality and morbidity rates in major hepatectomy still remain unsolved. Particularly, post-hepatectomy liver failure is a lethal complication [2]. Future liver remnant (FLR) volume needs to be >30% in normal livers and 50% in damaged livers in order to avoid liver failure [3]. In cases with insufficient FLR volume, portal vein embolization (PVE) generally has been performed to induce compensatory hypertrophy of the remnant liver and to improve safety of major hepatectomy [4]. Previous PVE studies demonstrated that FLR volume increased by 20–50% during 3–7-week interval period between PVE and hepatectomy [5-8]. However, various conditions, including hepatitis, cholestasis, and chemotherapy, are reported to affect remnant liver hypertrophy [7,9-12]. Meanwhile, 10–20% of cases become unresectable after an interval period because of tumor progression or insufficient remnant liver hypertrophy [13,14].

Recently, Schnitzbauer et al. [15] reported a novel strategy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), which induced marked and rapid remnant liver hypertrophy. Other studies have demonstrated its usefulness [16-18]. However, the indication for ALPPS should be restricted because of the complexity of the surgical procedure and the high

morbidity rate.

Early prediction of hypertrophy ratio after PVE may enable the identification of patients who will be refractory to PVE and may be useful in determining the indication for ALPPS.

Therefore, the aim of the present study was to clarify the factors that affect remnant liver hypertrophy after PVE and to establish a prediction formula for the hypertrophy ratio.

Methods

Study design

We performed a retrospective cohort study of patients with liver diseases who underwent preoperative PVE between January 2005 and December 2012 at the Department of Surgery, Kyoto University Hospital. In total, PVE was performed for the operation in 65 patients. Six patients were excluded from the analysis because of the following reasons: 5 patients underwent embolization of the portal branches of ≤ 1 segment; 1 patient was not performed post-PVE CT scan because exploratory laparoscopy revealed peritoneal dissemination. After the exclusion, 59 patients were analyzed in this study (fig. 1). Patients' diseases consisted of cholangiocarcinoma in 39 patients (66%), metastatic carcinoma in 10 patients (17%), hepatocellular carcinoma in 8 patients (14%), cystic tumor of the liver in 1 patient, and benign gallbladder tumor in 1 patient. This study was in accordance with the ethical guidelines for epidemiological research in Japan, and approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (approval code: E1737).

Indication for PVE and procedure

The indication for PVE was as follows: future liver remnant ratio to total liver (FLR%) below 30%, planned hepatopancreatoduodenectomy, or poor functional reserve [3]. PVE was routinely performed by the percutaneous transhepatic ipsilateral approach, with the contralateral

approach used only in patients for whom the ipsilateral approach was judged to be unsuitable. The embolization materials consisted of absolute ethanol (Dehydrated ethanol Mylan; Mylan, Tokyo, Japan), iodized oil (Lipiodol Ultra-Fluide; Terumo, Tokyo, Japan), and porous gelatin particles (Gelpart; Nippon KAYAKU, Tokyo, Japan) with or without detachable microcoils (Presidio and Cashmere; Codman, Johnson and Johnson, NJ, USA). Embolized portal branches were right branch in 47 patients (80%), right with branch of segment IV in 8 (14%), left branch in 1 (2%), and left with anterior branch in 3 (5%).

CT volumetry

Multi-slice CT scans were performed before and 3 weeks after PVE. Liver volume was measured by delineating the liver in each 1-mm thick slice on a workstation, AZE VirtualPlace Plus (AZE, Tokyo, Japan). FLR% and hypertrophy ratio were calculated using the following formula:

$$\text{FLR\%} = 100 \times \text{FLR [mL]} / (\text{total liver volume [mL]} - \text{tumor volume [mL]}); \text{hypertrophy ratio (\%)} = 100 \times (\text{FLR after PVE [mL]} - \text{FLR before PVE [mL]}) / \text{FLR before PVE [mL]}.$$

Predictive model for the hypertrophy ratio

Predictive factors for the hypertrophy ratio were detected by step-wise variable selection with Bayesian information criterion among the following variables: age; gender; FLR%; plasma

disappearance rate of indocyanine green (ICGK); platelet count; prothrombin activity; serum albumin; serum total bilirubin at the time of PVE (Bil at PVE) and the maximum value before PVE (Max Bil); and history of cholangitis, diabetes mellitus, and ≥ 6 cycles of systemic chemotherapy. Then the prediction formula for the hypertrophy ratio was set up with the detected predictive factors by multiple regression analysis. Male and female genders were defined as “1” and “0,” respectively. History of cholangitis, diabetes mellitus, and chemotherapy was defined as “1” if history existed and “0” if history did not exist. The ICG test was performed under the condition of serum total bilirubin < 5 mg/dL in all cases.

After detection of predictive factors, a 10-fold cross validation was performed for the predictive model. In brief, all patients were randomly divided into 10 groups. The prediction value of the hypertrophy ratio in 1 group was calculated with the prediction formula set up by multiple regression analysis of the other 9 groups, using the detected predictive factors. This calculation was repeated in turn, and then we evaluated calibration and discriminatory power of the predictive model. We constructed scatter plots of predicted and observed hypertrophy ratios to evaluate calibration and we used sensitivity and specificity to identify patients with the hypertrophy ratio $< 20\%$ as a criterion for discriminatory power.

Functional volume change was analyzed by technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin (^{99m}Tc -GSA)

scintigraphy to examine whether the prediction formula could reflect functional gain.

Statistical analysis

Data were expressed as mean \pm SD unless otherwise indicated. Volumetric differences before and after PVE were compared using the paired t-test, while other continuous variables were compared using the unpaired t-test. A 2-tailed P value <0.05 was considered significant. All analyses were performed using JMP software version 10 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' clinical course after PVE

Most patients experienced transient fever after PVE. Two patients experienced complicated hemorrhagic events (subcapsular hematoma and intra-abdominal hemorrhage), both of which were managed conservatively, and 1 was complicated with bile leakage, which was managed with percutaneous drainage. FLR volume significantly increased from 346 ± 126 mL ($29.2 \pm 9.5\%$) to 438 ± 144 mL ($37.5 \pm 10.6\%$, $P < 0.001$) in 3 weeks (median, 21 days; range, 14–99 days) after PVE. The mean hypertrophy ratio was $28.8 \pm 20.7\%$ (range, -22.0 – 105.1%) (fig. 2). Of those undergoing PVE, 5 patients did not undergo laparotomy because of tumor progression (3 patients), insufficient liver function (1 patient), and pulmonary embolism death (1 patient). Fifty-two patients (88%) underwent planned hepatectomy, while the other 2 patients with hilar cholangiocarcinoma underwent exploratory laparotomy because of local invasion in 1 patient and positive lavage cytology in the other patient (fig. 1).

Predictive factors and prediction formula

The mean age was 65.3 ± 9.5 (range, 33–84). There were 39 men and 20 women. Thirty-eight patients (64%) underwent biliary drainage for obstructive cholestasis, and 15 patients (25%) were complicated with cholangitis. Seven patients with colorectal liver metastasis received

systemic chemotherapy with a median 11 cycles (range, 6 – 29) of oxaliplatin or irinotecan regimen.

In simple regression analysis, FLR% ($P = 0.010$), ICGK ($P = 0.018$), Bil at PVE ($P = 0.028$) and

Max Bil ($P = 0.045$) were significant factors. In step-wise variable selection, the following 5

parameters were detected as predictive factors: ICGK ($P = 0.112$) as a positive factor and age ($P =$

0.015), FLR% ($P < 0.001$), Max Bil ($P < 0.001$), and history of chemotherapy ($P = 0.007$) as negative

factors (table 1). The following prediction formula was calculated:

$$\underline{101.6 - 0.78 \times \text{Age} - 0.88 \times \text{FLR}\% + 128 \times \text{ICGK} - 1.48 \times \text{Max Bil (mg/dL)} - 21.2 \times \text{Chemotherapy}}$$

The value obtained using this formula significantly correlated with the actual value ($r = 0.72$, $P <$

0.001) (fig. 3a). When the cut-off value was set at 20%, less value of the hypertrophy ratio was

predictable with 100% sensitivity and 90.9% specificity. Significant correlation was also observed in

each of the following diseases: cholangiocarcinoma ($r = 0.68$, $P < 0.001$), metastatic carcinoma ($r =$

0.93 , $P < 0.001$), and hepatocellular carcinoma ($r = 0.78$, $P = 0.040$). A 10-fold cross validation also

showed significant correlation between the observed and predicted values ($r = 0.62$, $P < 0.001$), and

the slope of the regression line was 0.87 , indicating the calibration of the prediction formula was

good (fig. 3b). The hypertrophy ratio below 20% in 10-fold cross validation also was predictable

with 100% sensitivity and 90.9% specificity.

Three outliers in the prediction of the hypertrophy ratio below or above 20% are shown in table 2. All 3 patients presented much less hypertrophy ratio than predicted, and 2 of 3 patients

experienced complications of PVE, intra-abdominal hemorrhage and bile leakage, which might be the causes of poor response to PVE.

^{99m}Tc -GSA scintigraphy was performed both before and after PVE in 20 patients, 7 patients with prediction values below 20% and 13 patients with values above 20%. The increase in the uptake ratio of the remnant liver (uptake ratio of remnant liver after PVE – before PVE) was significantly lower in patients with prediction values below 20% than in those with values above 20% ($6.8 \pm 4.2\%$ vs. $20.8 \pm 15.3\%$, $P = 0.030$; fig. 4). These results indicated that the formula established in this study could predict the degree of liver hypertrophy in an appropriate manner, reflecting the result of the ^{99m}Tc -GSA scintigraphy, and might be useful for clinical application.

Discussion

In the present study, we analyzed a prediction formula for the hypertrophy ratio after PVE and explored the possibility of its application to a new strategy for hepatobiliary surgery. There have been several reports on prediction of remnant liver hypertrophy after PVE. Imamura et al. [11] showed that diabetes mellitus, high bilirubin level at the time of PVE, male sex and FLR volume were the negative factors for remnant liver hypertrophy. A large FLR means small volume of embolized liver parenchyma, thus less impact on volume shift. Several studies, including ours, supported this finding [7,19,20]. Cholestasis is also a known inhibitor of hepatic regeneration [10], and Imamura et al. emphasized the influence of the bilirubin level at the time of PVE on FLR hypertrophy [11]. However, we first demonstrated the significance of maximum bilirubin level before biliary drainage as a negative predictive factor for the hypertrophy ratio, which suggested that the liver once exposed to high levels of cholestasis had attenuated regenerative capacity even if followed by adequate biliary drainage at the time of PVE. However, best available biliary drainage should be performed before PVE, as portal flow occlusion under high levels of cholestasis might cause severe liver failure owing to the enhancement of hepatocyte apoptosis [10].

Novel chemotherapeutic drugs against colorectal cancer such as oxaliplatin and irinotecan have extended the pool of patients indicated for liver resection, which has increased the need for PVE including 2-staged hepatectomy [21]. Meanwhile, oxaliplatin and irinotecan were reported to

induce severe liver injury known as sinusoidal obstruction syndrome and steatohepatitis, respectively, and to impair liver regeneration [12,22,23]. Additionally, in the present study, history of chemotherapy containing these drugs was indicated as a strong negative predictive factor (regression coefficient = -21.2). Although we could not clarify the association between pathological findings of these liver injuries and the hypertrophy ratio because of the small number of patients with liver metastasis, liver biopsy might be considered before PVE to confirm the severity of liver injury in patients receiving multiple chemotherapy cycles.

Regarding safety of major hepatectomy, functional volume as well as morphologic volume of FLR is an important matter. In ^{99m}Tc-GSA scintigraphy, uptake ratio reflects separate functional volume and is suited for the evaluation of functional volume shift after PVE [24]. Our data indicated that the liver with a lower prediction value of the hypertrophy ratio gained less liver functional reserve, which was consistent with the idea that prediction of morphologic volume change after PVE also reflects functional volume change. Moreover, this finding indicated that another imaging modality validated the prediction formula for the hypertrophy ratio measured by CT scan.

Recently, several authors reported that associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) induced marked and rapid remnant liver hypertrophy and could reduce the risk of post-hepatectomy liver failure [15-18]. This novel technique is expected to be a breakthrough in the field of hepatobiliary surgery. However, ALPPS is characterized by the

complexity of the surgical procedure and the high morbidity rate, including bile leakage[15].

Therefore, the indication should be restricted. The proposed indication for ALPPS is bilateral liver metastasis, very small FLR of <25%, or salvage for poor response to PVE [18,25]. Knoefel et al.

[18] demonstrated that ALPPS for patients with poor response to PVE induced comparable FLR

hypertrophy to those who underwent direct ALPPS without PVE, indicating the effectiveness of

salvage ALPPS for poor responders to PVE. However, as PVE was reported to accelerate tumor

proliferation during the waiting time [20], useless PVE should be avoided. Our prediction formula

could well predict both morphologic and functional liver volume changes, especially in poor

responders to PVE. Because poor response to PVE is regarded as a risk factor for post-hepatectomy

liver failure [7,26], those patients might need additional FLR volume to avoid liver failure.

Therefore, patients with lower predictive hypertrophy ratios, who would be predicted to gain

insufficient FLR volume both morphologically and functionally if PVE was performed, might

benefit from direct ALPPS without PVE. This strategy might enable those patients to achieve

sufficient FLR hypertrophy without tumor progression during the waiting period.

There are several limitations in the present study. First, the sample size was relatively small. Second, we could not show the relationship between the predictive hypertrophy ratio and postoperative outcomes. Postoperative outcome also depends on underlying liver disease and subsequent liver damage, lymphadenectomy, biliary or vascular reconstruction, and concomitant

pancreatectomy. Therefore, we considered it inadequate to associate the prediction of the hypertrophy ratio with postoperative outcome unconditionally, as we studied a heterogeneous population. Third, prospective or external validation is needed to further verify the prediction formula for application in clinical practice.

In conclusion, we demonstrated that a prediction formula could predict the hypertrophy ratio after PVE, and FLR volume can be calculated with this formula. This may provide a new therapeutic strategy for major hepatectomy, including ALPPS.

Acknowledgements

The authors declare no conflict of interest.

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Figure legends

Fig. 1. Population of the study, the surgical procedures, and the reasons for unresectability after PVE

HPD = Hepatopancreatoduodenectomy

Fig. 2. Future liver remnant volume change after PVE

Fig. 3. a Correlation between predictive and actual hypertrophy ratio: Predictive hypertrophy ratio

was significantly correlated with actual hypertrophy ratio ($r = 0.72$, $P < 0.001$). Hypertrophy ratio

below 20% was predictable with a sensitivity of 100% and specificity of 90.9%. Significant

correlation was also observed in each of the following diseases: cholangiocarcinoma ($r = 0.68$, $P <$

0.001), metastatic carcinoma ($r = 0.93$, $P < 0.001$), and hepatocellular carcinoma ($r = 0.78$, $P =$

0.040). b Ten-fold cross validation: Ten-fold cross validation also showed significant correlation ($r =$

0.62 , $P < 0.001$), and the slope of the regression line was 0.87 .

CC = Cholangiocarcinoma, MC = Metastatic carcinoma, HCC = Hepatocellular carcinoma

Fig. 4. Change in uptake ratio of ^{99m}Tc -GSA scintigraphy. a Uptake ratio before and after PVE:

There was no significant difference in uptake ratio at baseline and after PVE between patients with

predictive hypertrophy ratio below and above 20%. b Increase in uptake ratio after PVE: Patients

with predictive hypertrophy ratio below 20% gained less functional volume shift than those with the ratio above 20% ($6.8 \pm 4.2\%$ vs. $20.8 \pm 15.3\%$, $P = 0.030$).

PHR = Predictive hypertrophy ratio

**65 patients underwent PVE
between 2005 and 2012**

6 patients were excluded from the analysis
5; Embolized portal branch of ≤ 1 segment
1; Absence of post-PVE CT scan

**59 patients
were analyzed**

**5 patients did not undergo
laparotomy**

3; Tumor progression
1; Insufficient liver function
1; Pulmonary embolism death

**54 patients
underwent
laparotomy**

**2 patients did not undergo
hepatectomy**

1; Local invasion
1; Positive lavage cytology

52 patients underwent planned hepatectomy

26; Right lobectomy
16; Right trisegmentectomy
6 ; Extended right lobectomy
2 ; Left trisegmentectomy
1 ; Extended left lobectomy
1 ; Left lobectomy
9; Concomitant pancreatectomy (HPD)

Fig. 1.

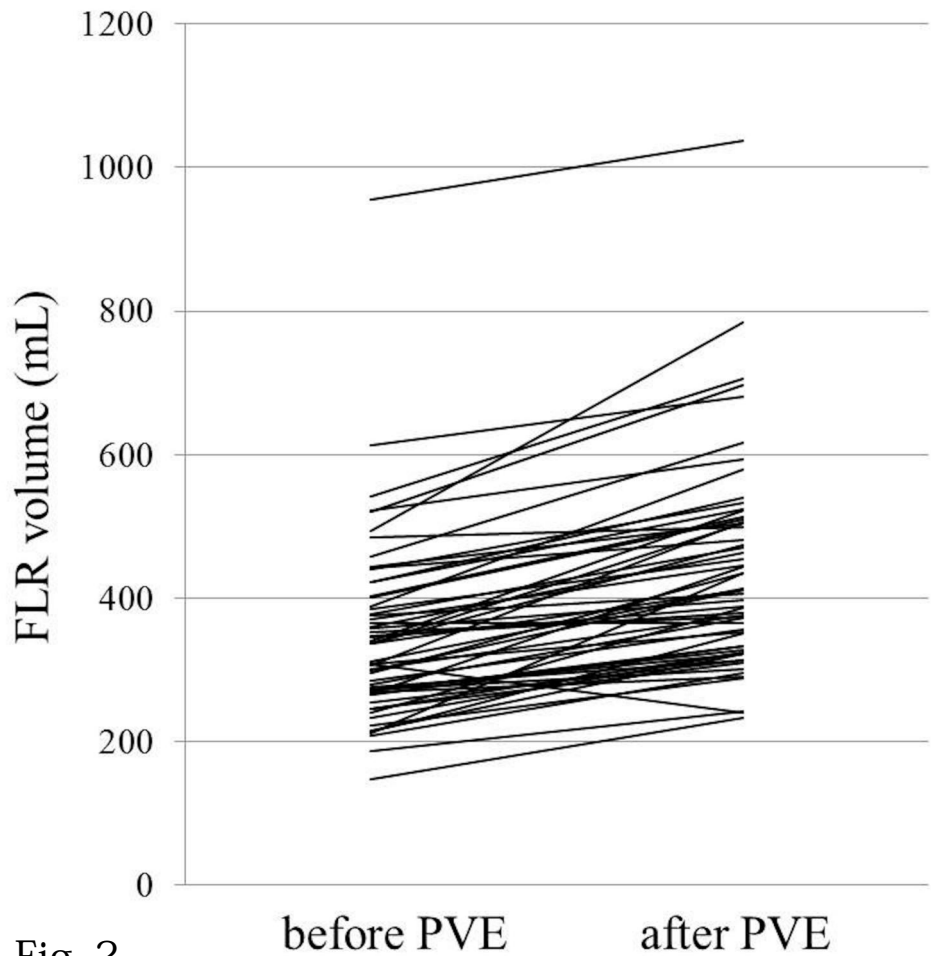
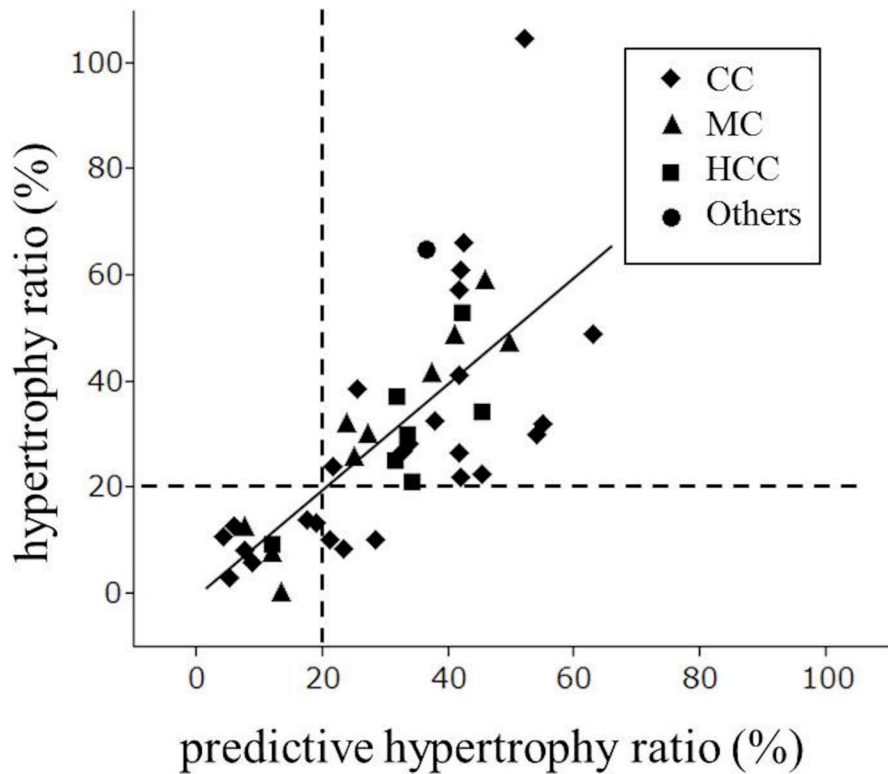
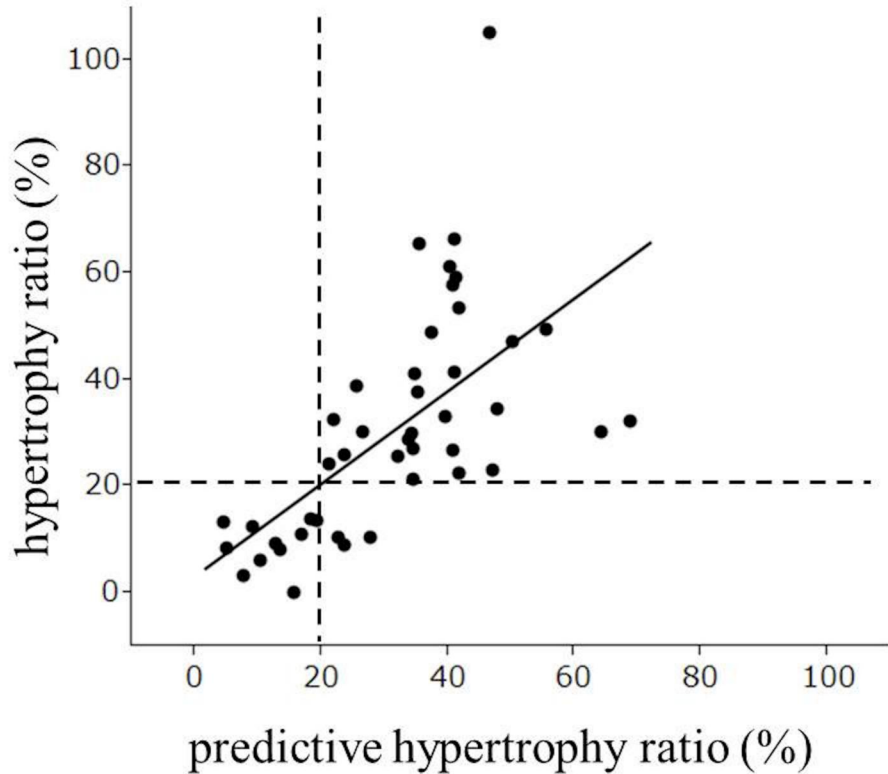


Fig. 2.

a**b**

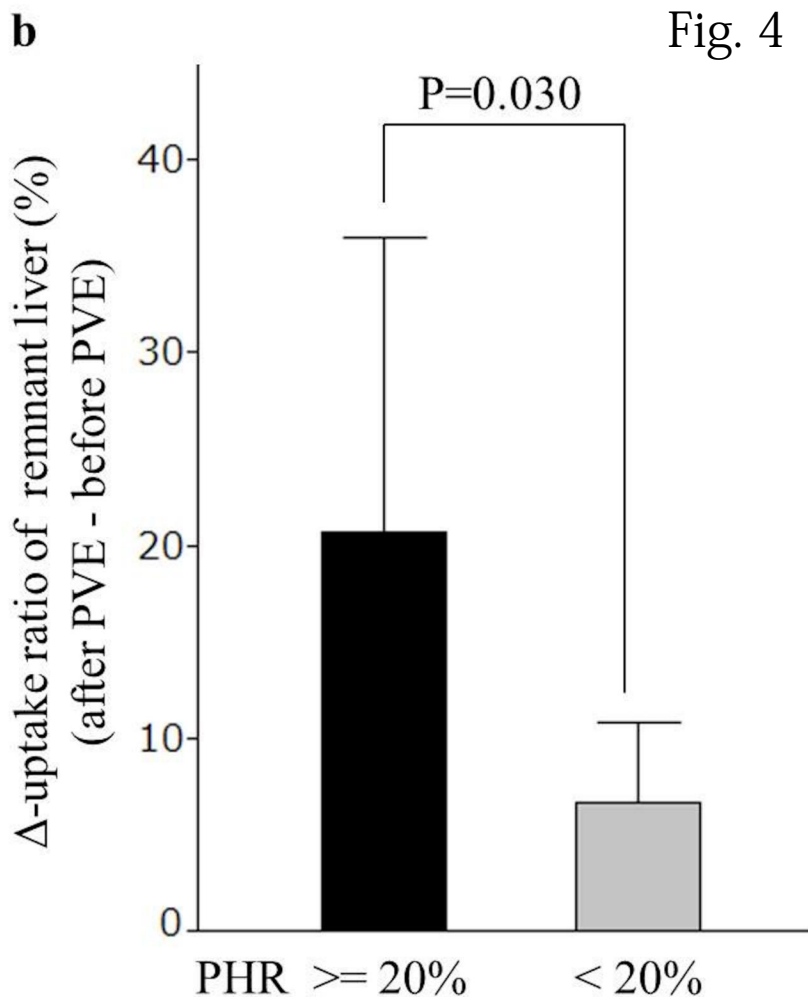
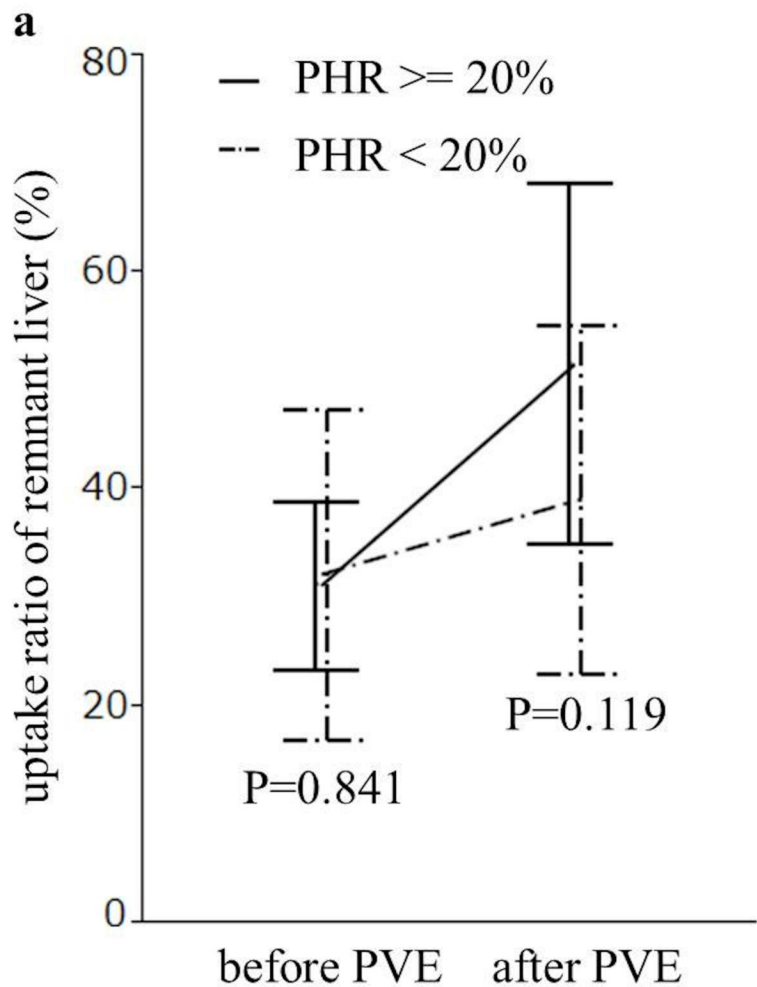


Table 1. Multiple regression analysis

Variables	Mean \pm SD	β	95% CI [L, U]	P value
Age	65.3 \pm 9.5	<u>-0.78</u>	<u>-1.40, -0.16</u>	<u>0.015</u>
FLR%	29.2 \pm 9.5	-0.88	<u>-1.36, -0.41</u>	<0.001
ICGK	0.14 \pm 0.03	<u>128</u>	<u>-31.2, 288</u>	<u>0.112</u>
Max Bil (mg/dL)	<u>7.37 \pm 8.95</u>	<u>-1.48</u>	<u>-2.23, -0.73</u>	<0.001
Chemotherapy (+/-)	7 / 52	<u>-21.2</u>	<u>-36.1, -6.28</u>	<u>0.007</u>

β = Regression coefficient, 95% CI = 95% confidence interval, L =

Lower confidence limit, U = Upper confidence limit

Table 2. Outliers of the prediction

Age	Sex	Diagnosis	FLR%	ICGK	Max Bil	CT	PHR %	AHR %	Remarks
70	F	Hilar CC	21	0.149	13.4	no	27.5	10.4	Non-medicated diabetes
74	M	ICC	27	0.117	8.2	no	22.9	8.9	Bile leakage
84	F	Hilar CC	33	0.127	1.7	no	20.7	10.4	Intra-abdominal hemorrhage

CT = Chemotherapy, PHR = Predictive hypertrophy ratio, AHR = Actual hypertrophy ratio, CC = Cholangiocarcinoma, ICC = Intrahepatic cholangiocarcinoma
